PCT/EP2004/011963

21 10. 2004

EP04/11963

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

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Signed Andrew Gerrey

Dated 6 October 2004

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
G
24 OCT 2003
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The Patent Office

27OCT03 E847258-1 D02029
P01/7700 0.00-0324886.1

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

JAF/PB60557P

2. Patent application number
(The Patent Office will fill this part in)

0324886.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX. UB6 ONN
GB

Patents ADP number *(if you know it)*

4735887003

If the applicant is a corporate body, give the country/state of its incorporation

GB

4. Title of the invention

MEDICINAL COMPOUNDS

5. Name of your agent *(if you have one)*

ATTORNEY NAME

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY (CN9 25.1)
980 GREAT WEST ROAD
BRENTFORD
MIDDLESEX
TW8 9GS

Patents ADP number *(if you know it)*

8072555006

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	72 only
Claim(s)	7
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) JULIA A FLORENCE, Agent for the Applicants Julia Florence Date 23 October 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

CONTACT NAME Lesley Wells

TEL 01438 768599

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered YES in part 8, a Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

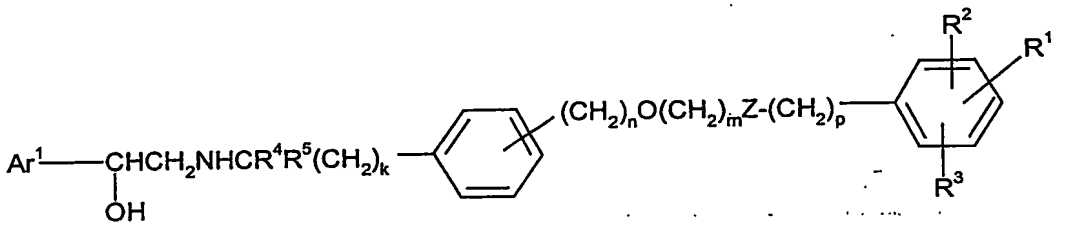
Medicinal Compounds

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2-adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2-adrenoreceptor agonists are effective bronchodilators, the duration of action is approximately 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2-adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

n is an integer of from 1 to 4;
m is an integer of from 2 to 4;
p is an integer of from 1 to 4, preferably 1;
k is an integer from 1 to 3;
Z is O or CH_2-

R^1 is selected from hydrogen, C_{1-6}alkyl, hydroxy, cyano, nitro, halo, C_{1-6}haloalkyl, XCO_2R^8, $-XC(O)NR^7R^8$, $-XNR^6C(O)R^7$, $-XNR^6C(O)NR^7R^8$, $-XNR^6C(O)NC(O)NR^7R^8$, $-XNR^6SO_2R^7$, $-XSO_2NR^9R^{10}$, XSR^6, $XSOR^6$, XSO_2R^6, $-XNR^7R^8$, $-XNR^6C(O)OR^7$,
or R^1 is selected from -X-aryl, -X-hetaryl, or -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, $-NR^6C(O)R^7$, SR^6, SOR^6, $-SO_2R^6$, $-SO_2NR^9R^{10}$, $-CO_2R^8$, $-NR^7R^8$, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

X is $-(CH_2)_q-$ or C_{2-6} alkenylene;

q is an integer from 0 to 6, preferably 0 to 4;

R^6 and R^7 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)- and R^6 and R^7 are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, $-NHC(O)(C_{1-6}$alkyl), $-SO_2(C_{1-6}$alkyl), $-SO_2$(aryl), $-CO_2H$, and $-CO_2(C_{1-4}$alkyl), $-NH_2$, $-NH(C_{1-6}$alkyl), aryl(C_{1-6}alkyl)-, aryl(C_{2-6}alkenyl)-, aryl(C_{2-6}alkynyl)-, hetaryl(C_{1-6}alkyl)-, $-NHSO_2$aryl, -NH(hetarylC_{1-6}alkyl), $-NHSO_2$hetaryl, $-NHSO_2(C_{1-6}$alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

R^8 is selected from hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl;

or R^7 and R^8, together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7- membered nitrogen – containing ring;

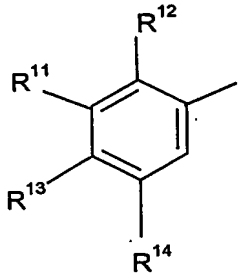
R^9 and R^{10} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)-, or R^9 and R^{10}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;
and R^9 and R^{10} are each optionally substituted by one or two groups independently selected from halo, C_{1-6}alkyl, and C_{3-7}cycloalkyl, C_{1-6}haloalkyl;

R^2 is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo, aryl, aryl(C_{1-6}alkyl)-, C_{1-6}haloalkoxy, and C_{1-6}haloalkyl;

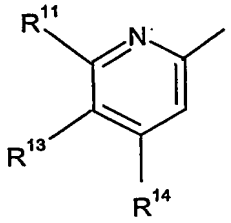
R^3 is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo, aryl, aryl(C_{1-6}alkyl)-, C_{1-6}haloalkoxy, and C_{1-6}haloalkyl; and

R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4

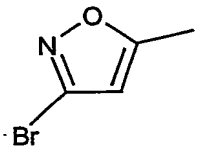
Ar^1 is a group selected from



(a)

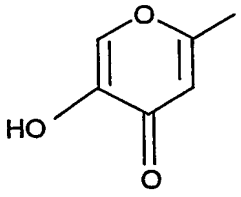


(b)



(c)

and



(d)

wherein R^{11} represents hydrogen, halogen, $-(CH_2)_rOR^{15}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}SO_2R^{16}$, $-SO_2NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$,
and R^{12} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{11} represents $-NHR^{18}$ and R^{12} and $-NHR^{18}$ together form a 5- or 6- membered heterocyclic ring;

R^{13} represents hydrogen, halogen, $-OR^{15}$ or $-NR^{15}R^{16}$;

R^{14} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{15}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$;

R^{15} and R^{16} each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$ and $-OC(O)NR^{15}R^{16}$, R^{15} and R^{16} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{17} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

r is zero or an integer from 1 to 4.

In the compounds of formula (I), the group R^1 is suitably selected from hydrogen, C_{1-4}alkyl, hydroxy, halo, $-NR^6C(O)NR^7R^8$, and $-NR^6SO_2R^7$ wherein R^6 and R^7 are as defined above or more suitably wherein $R^6$is hydrogen and R^7 is selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, and aryl and is optionally substituted as described above.

Where R^1 is $-XNR^6C(O)NR^7R^8$, R^6 and R^7 may, together with the -NC(O)N- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an imidazolidine ring, such as imidazolidine-2,4-dione.

Where R^1 is $-XNR^6C(O)OR^7$, R^6 and R^7 may, together with the -NC(O)O- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an oxazolidine ring, such as oxazolidine-2,4-dione.

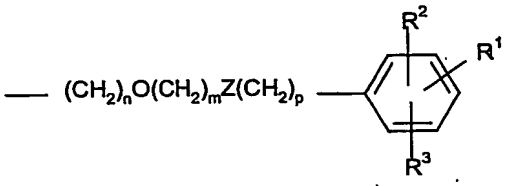
Where R^1 is $-XC(O)NR^7R^8$ or $-XNR^6C(O)NR^7R^8$, R^7 and R^8 may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring.

In the compounds of formula (I) wherein the group R^1 is substituted by $R^6$and/or R^8, R^6 and/or R^8 are suitably hydrogen.

In the compounds of formula (I), R^4 and R^5 are preferably independently selected from hydrogen and methyl.

In the compounds of formula (I) R^2 and R^3 preferably each represent hydrogen.

Preferably the moiety

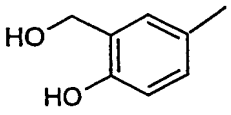


is attached to the meta position of the 'central' phenyl ring, relative to the $-NHCR^4R^5CH_2-$ moiety.

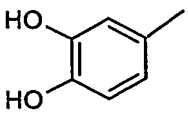
In the compounds of formula (I) the group Ar^1 is preferably selected from groups (a) and (b) above. In said groups (a) and (b), when R^{11} represents halogen this is preferably chlorine or fluorine. R^{15} and R^{16} preferably each independently represent hydrogen or methyl. R^{17} preferably represents substituted phenyl. The integer r preferably represents zero or 1. Thus for example $-(CH_2)_rOR^{15}$ preferably represents OH or $-CH_2OH$;
$NR^{15}C(O)R^{16}$ preferably represents $-NHC(O)H$;
$-SO_2NR^{15}R^{16}$ preferably represents $-SO_2NH_2$ or SO_2NHCH_3;
$NR^{15}R^{16}$ preferably represents $-NH_2$;
$-OC(O)R^{17}$ preferably represents substituted benzoyloxy eg. $OC(O)-C_6H_4-(p-CH_3)$; and
$-OC(O)N\ R^{15}\ R^{16}$ preferably represents $OC(O)N(CH_3)_2$.

When R^{11} represents NHR^{18} and together with R^{12} forms a 5- or 6- membered heterocyclic ring $-NHR^{18}-R^{12}-$ preferably represents a group:
$-NH-CO-R^{19}-$ where R^{19} is an alkyl, alkenyl or alkyloxy group;
$-NH-SO_2R^{20}-$ where R^{20} is an alkyloxy group;
$-NH-R^{21}-$ where R^{21} is an alkyl or alkenyl group optionally substituted by $COOR^{22}$ where R^{22} is C_{1-4} alkyl; or
-NH-CO-S-;
wherein said alkyl, and alkenyl groups and moieties contain 1 or 2 carbon atoms.

Particularly preferred groups (a) and (b) may be selected from the following groups (i) to (xxi):



(i)



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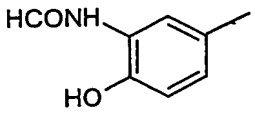

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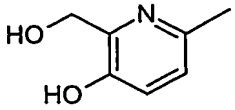

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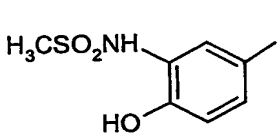

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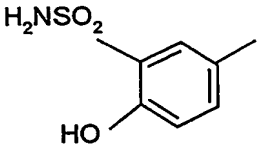

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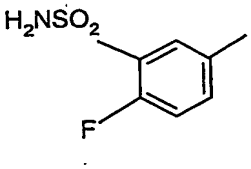

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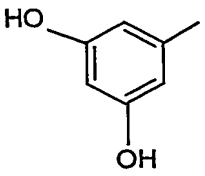

(viii)

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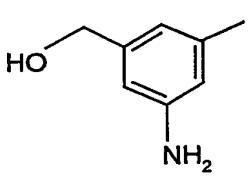

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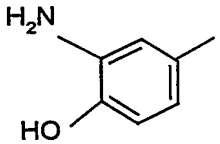

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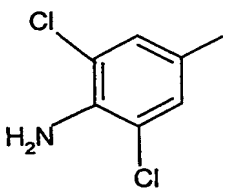

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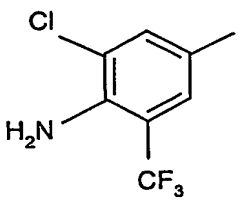

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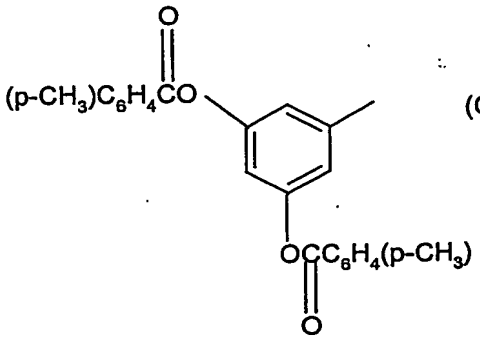

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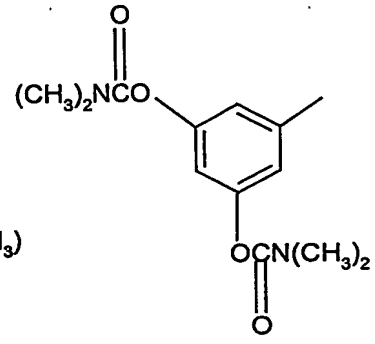

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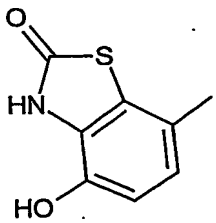

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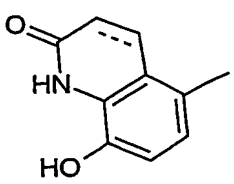

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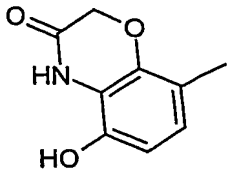

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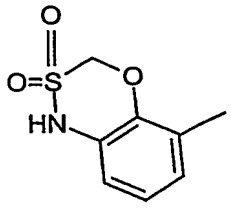
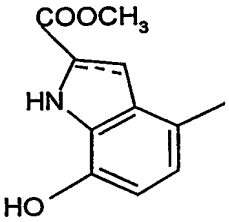


(xviii)



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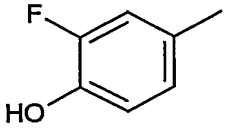
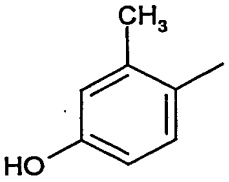


(xx)



(xxi)

wherein the dotted line in (xvi) and (xix) denotes an optional double bond.

Most preferably Ar^1 represents a group (i).

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

The compounds of formula (I) include an asymmetric centre, namely the carbon atom of the

group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions. Preferably, the compounds of the invention are in the form of the (R) enantiomers.

Similarly, where R^4 and R^5 are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Thus the compounds of formula (I) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl , methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters of the compounds of formula (I) may have a hydroxyl group converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, or amino acid ester.

As mentioned above, the compounds of formulae (I) are selective β_2-adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2-agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

Therefore, compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2-adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin

diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated. In particular, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The

compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg, e.g. 0.05mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 10mg per day and preferably 0.01mg to 1mg per day, most preferably e.g. 0.05mg to 0.5mg per day.

While it is possible for the compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di or poly-saccharides (eg. lactose or starch). Use of lactose is preferred.

Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) or (Ia) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134, US Patent Nos. 6,632,666, 5,860,419, 5,873,360 and 5,590,645 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Patent No.s 4,778,054, 4,811,731, 5,035,237, the disclosures of which are hereby incorporated by reference) or

metered in use (eg as in Turbuhaler, see EP 69715 or in the devices described in US Patents No. 6,321,747 the disclosures of which are hereby incorporated by reference). An example of a unit-dose device is Rotahaler (see GB 2064336 and US Patent No. 4,353,656, the disclosures of which are hereby incorporated by reference). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) or (Ia) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired

fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose an acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g.

antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β_2-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, more preferably 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2-adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC_{50} ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/57599 for another description of said assay.

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^{3}H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[^{3}H]-cAMP as the substrate.

Most preferred are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC_{50} ratio of 0.1 or greater.

Other compounds of interest include:
Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from

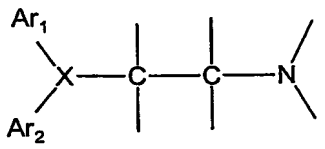
Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:
Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.
Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.
Hyoscyamine (*d*, *l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.
Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt- CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chloropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I), or a salt, solvate, or physiologically functional derivative thereof which comprises a process (a), (b), (c) or (d) as defined below followed by the following steps in any order:

(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer or diastereoisomer from a mixture of enantiomers or diastereoisomers;

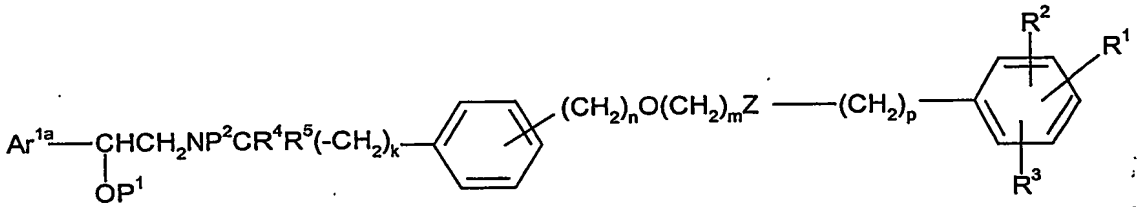
(iii) optional conversion of the product to a corresponding salt, solvate,

(iv) optional conversion of a group R^1, R^2 and/or R^3 to another group R^1, R^2 and/or R^3,

or physiologically functional derivative thereof.

In the following description of synthetic routes, R^1, R^2, R^3, R^4, R^5, Z, m, n and p are as defined for formula (I) and R^{11}, R^{12}, R^{13} and R^{14} are as defined for formula (II) below unless indicated otherwise.

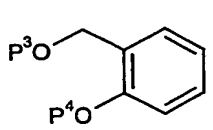
In one general process (a), a compound of formula (I), may be obtained by deprotection of a protected intermediate, for example of formula (II):



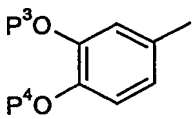
(II)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, Z, k, m, n and p are as defined for the compounds of formula (I), and wherein Ar^{1a} is Ar^1 or a protected form thereof and P^1 and P^2 each independently represents either hydrogen or a protecting group provided that the compound of formula (II) contains at least one protecting group.

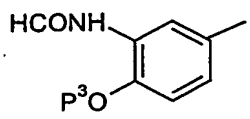
Optionally protected forms Ar^{1a} of the preferred groups Ar^1 may be selected from:



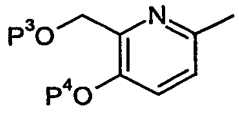
(ia)



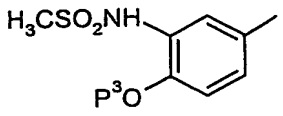
(iia)



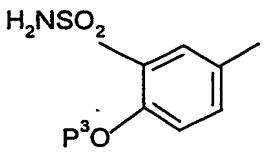
(iiia)



(iva)

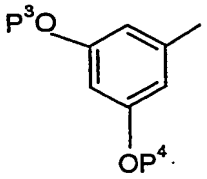


(va)

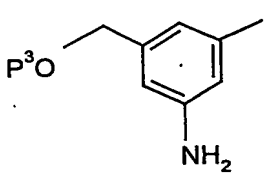


(via)

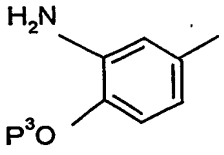
(viia)



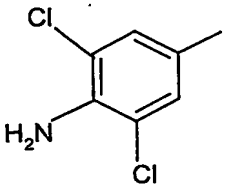
(viiia)



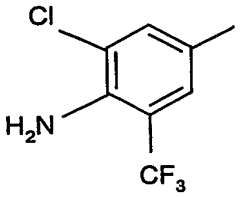
(ixa)



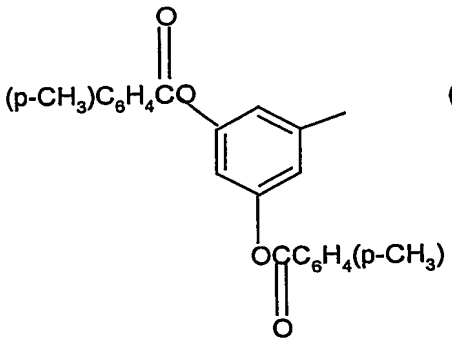
(xa)



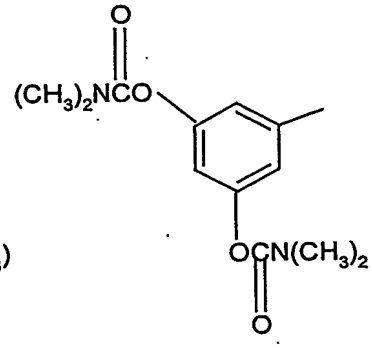
(xia)



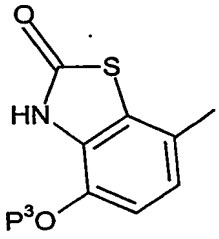
(xiia)



(xiiia)

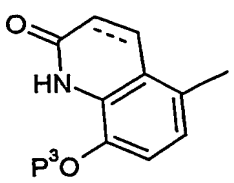


(xiva)

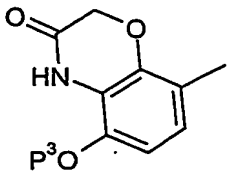


(xva)

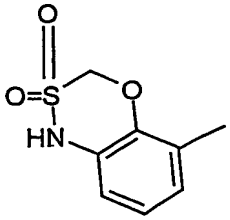
5



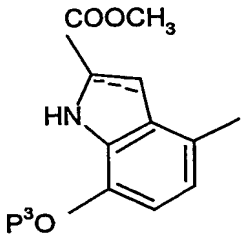
(xvia)



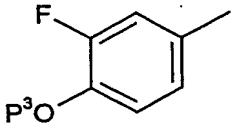
(xviia)



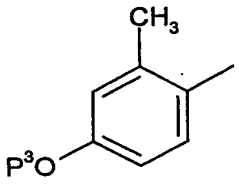
(xviiia)



(xixa)



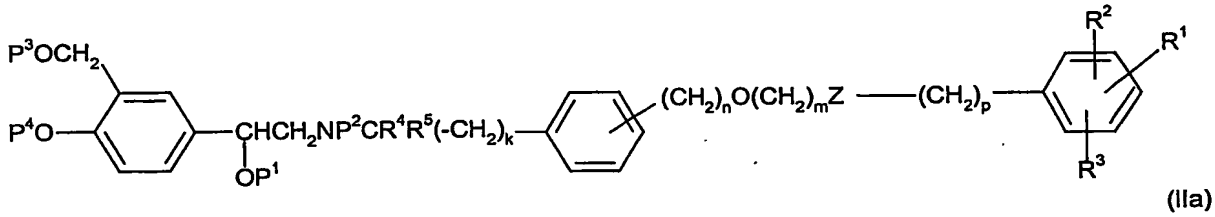
(xxa)



(xxia)

wherein P^3 and P^4 are each independently selected from hydrogen or a protecting group, and the dotted line in (xvia) and (xixa) denotes an optional double bond. It will be appreciated that when Ar^1 represents a group of structure (vii), (xi), (xii), (xiii) or (xiv) no protection of Ar^1 is required.

In one process (aa) according to the invention there is provided deprotection of a compound of formula (IIa)



(IIa)

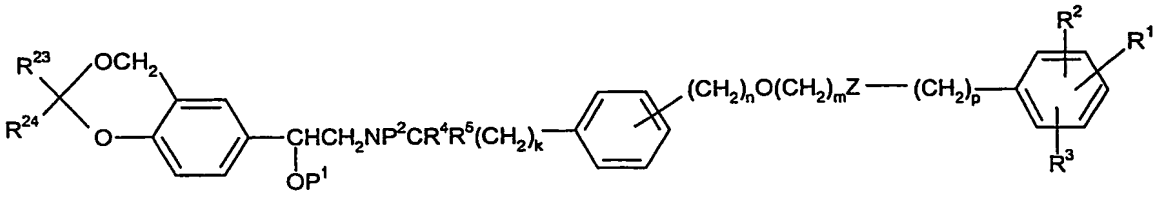
or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, Z, P^1, P^2, k, m, and p are as defined for the compounds of formula (II), and P^3 and P^4 are each independently either hydrogen or a protecting group provided that at least one of P^2, P^3 and P^4 is a protecting group and P^1 is either hydrogen or a protecting group.

Suitable protecting groups P^1-P^4 may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by P^3 and P^4 are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by P^2 include benzyl, α-methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the –CH(OH) group may be orthogonally protected as – $CH(OP^1)$ using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene and Peter G M Wuts (see above).

The deprotection to yield a compound of formula (I), may be effected using conventional techniques. Thus, for example, when P^3, P^4, and/or P^2 is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

When P^3 and/or P^4 is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R^{13} may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene and Peter G M Wuts (see above). In a particular embodiment of process (a), when Ar^1 represents a group (i) or (iv) P^3 and P^4 may together represent a protecting group as in the compound of formula (III):



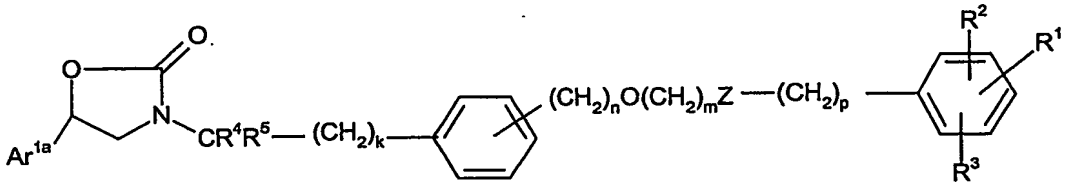
(III)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, P^1, Z, k, m, n and p are as defined for the compound of formula (I), and R^{23} and R^{24} are independently selected from hydrogen, C_{1-6}alkyl, or aryl or R^{23} and R^{24} together form a carbocyclic ring eg. containg from 5 to 7 carbon atoms. In a preferred aspect, both R^{23} and R^{24} are methyl, or one of R^{23} and R^{24} is hydrogen and the other is phenyl.

A compound of formula (III) may be converted to a compound of formula (I), by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

It will be appreciated that the protecting groups P^3, P^4, P^2 and P^1 (including the cyclised protecting group formed by P^3 and P^4 as depicted in formula (III) may be removed in a single step or sequentially. The precise order in which protecting groups are removed will in part depend upon the nature of said groups and will be readily apparent to the skilled worker. Preferably, when P^3 and P^4 together form a protecting group as in formula (III) this protecting group is removed together with any protecting group on the CH(OH) moiety, followed by removal of P^2.

A compound of formula (II) or formula (III) wherein P^1 and P^2 are hydrogen may be prepared from a corresponding compound of formula (IV):

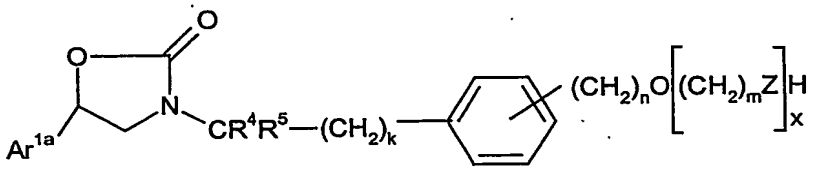


(IV)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, Ar^{1a}, Z, k, m, n and p are as defined for the compound of formula (II) or (III).

The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

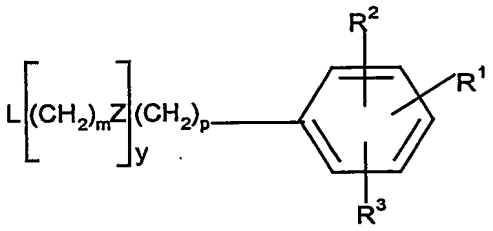
A compound of formula (IV) may be prepared by reacting a compound of formula (V):



(V)

wherein Ar^{1a}, R^4, R^5, Z, k, n and m are as defined for formula (II) and x is zero or 1;

with a compound of formula (VI):



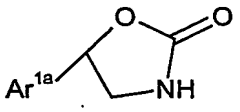
(VI)

wherein R^1, R^2, R^3, Z, m and p are as defined for formula (II), L is a leaving group such as halo (typically chloro, bromo or iodo) or a sulphonate eg. alkylsulphonate (typically methanesulphonate), and y represents 1 or zero such that the sum of x and y is 1. When x is 1, Z represents O.

The reaction of formula (V) and formula (VI) is advantageously effected in the presence of a base such as sodium hydride.

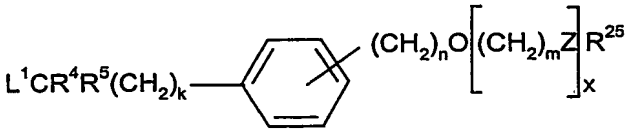
Compounds of formula (VI) are commercially available or may be prepared by methods well known to a person skilled in the art.

A compound of formula (V) may be prepared by coupling a compound of formula (VII):



(VII)

or a salt or solvate thereof, wherein Ar^1 is defined for the compound of formula (II) with a compound of formula (VIII):



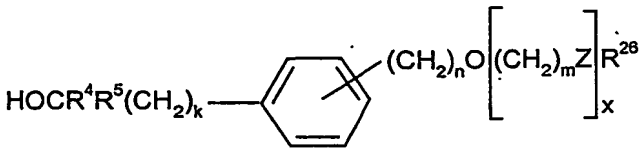
(VIII)

wherein x is zero or 1, L^1 is a leaving group, for example a halo group, (typically bromo or iodo) or a sulphonate such as an alkyl sulphonate (typically methanesulphonate) an aryl sulphonate (typically toluenesulphonate) or a haloalkylsulphonate (typically trifluoromethane sulphonate), and R^{25} is a hydroxyl protecting group, such as an acyl group. The group R^{25} may be removed by standard methods; alternatively, the R^{25} protecting group may be left in place and the protected compound may be utilised directly in the reaction with formula (VI).

The coupling of a compound of formula (VII) with a compound of formula (VIII) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as cesium carbonate, in an aprotic solvent, for example N,N-dimethylformamide. The protecting group R^{25} may be removed using standard methods, using eg. potassium trimethylsilanolate or sodium hydroxide. Those skilled in the art will appreciate that when potassium silanolate is employed then it is preferable to use only 1 equivalent and mild reaction conditions (room temperature) as an excess of this reagent and high temperature will result in cleavage of the oxazolidinone ring.

A compound of formula (VII) may be prepared for example by the method described in WO02/066422.

A compound of formula (VIII) may be prepared from a compound of formula (IX):



(IX)

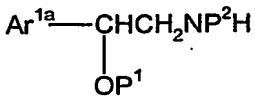
wherein x is zero or 1 and R^{26} is a hydroxyl protecting group such as aralkyl, typically benzyl, by conventional chemistry, for example by conversion of the hydroxyl group to a mesylate which may itself be converted to bromo by addition of a salt such as tetraalkylammonium bromide in a solvent such as acetonitrile, followed by removal of the protecting group R^{26} using standard conditions eg. hydrogenation in the presence of palladium on charcoal, and then introduction of R^{25}, for example by reaction with an acyl anhydride.

Compounds of formula (IX) wherein x is zero are known in the art or can readily be prepared by the skilled person using standard methods.

Compounds of formula (IX) wherein x is 1 may be prepared from a corresponding compound wherein x is zero by reaction with an appropriate alkylating agent.

Compounds of formulae (II) or (III) may also be prepared according to the general methods described below.

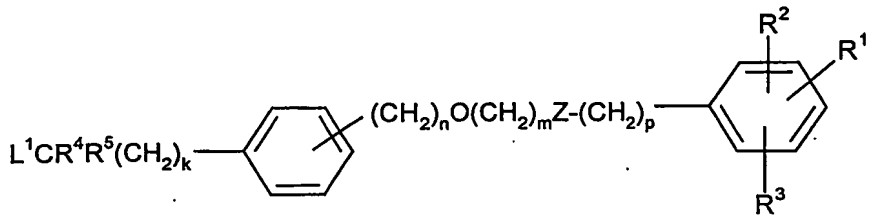
In a further process (b) a compound of formula (I), may be obtained by alkylation of an amine of formula (X):



(X)

wherein Ar^{1a} is defined for compounds of formula (II) P^1 and P^2 are each independently either hydrogen or a protecting group, for example as described hereinabove for compounds of formula (II) and (III);

with a compound of formula (XI):



(XI)

wherein L^1 is a leaving group as herein before defined for the compound of formula (VIII); followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II) and (III). For speed of reaction, L^1 is preferably bromo or is converted to bromo in situ, from the corresponding compound wherein L^1 is methanesulfonate, for example by addition of tetrabutylammonium bromide to the reaction mixture. In this process P^2 is preferably hydrogen.

A compound of formula (I), may be formed directly (when in the compound of formula (X) P^3, P^4, P^2 and P^1 are each hydrogen) or via a compound of formula (II) or (III) which may or may not be isolated (when in the compound of formula (X) at least one of P^3, P^4, P^2 and P^1 is a protecting group).

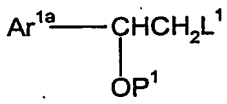
The reaction of compounds of formulae (X) and (XI) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example N,N-dimethylformamide, or acetonitrile.

Compounds of formula (X) are known in the art (for example EP-A 0947498) or may be readily prepared by a person skilled in the art, using known methods, for example as described in WO02/066422.

Further details concerning preparation of compounds (X) wherein Ar^1 is a group (v) can be found in DE3524990; concerning the preparation of compounds (X) wherein Ar^1 is a group (ii), (viii), and (xvi) in EP-A-162576; concerning the preparation of compounds (X) wherein Ar^1 is a group (iv) in EP-A-220054; concerning the preparation of compounds (X) wherein Ar^1 is a group (xi) in GB2165542 and concerning the preparation of compounds (X) wherein Ar^1 is a group (c) in GB2230523.

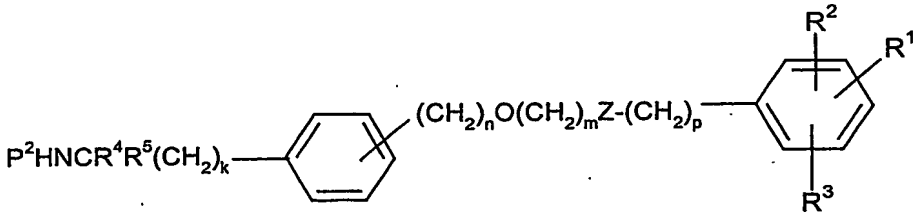
Compounds of formula (XI) may be prepared by general methods described hereinabove, as will be evident to a person skilled in the art, for example using methods similar to those used in the preparation of compounds (IX) and the reaction of compounds (V) and (VI).

In a further process (c) a compound of formula (I), may be prepared by reacting a compound of formula (XII):



(XII)

wherein Ar^{1a} as defined for compounds of formula (II) and P^1 is as hereinbefore defined and L^1 is a leaving group, with an amine of formula (XIII):



(XIII)

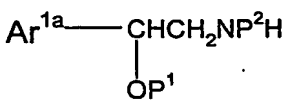
followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II).

The reaction may be effected using conventional conditions for such displacement reactions.

Compounds of formula (XII) may be prepared by methods known in the art.

Compounds of formula (XIII) may be prepared by reacting a compound of formula (XI) with an amine P^2NH_2.

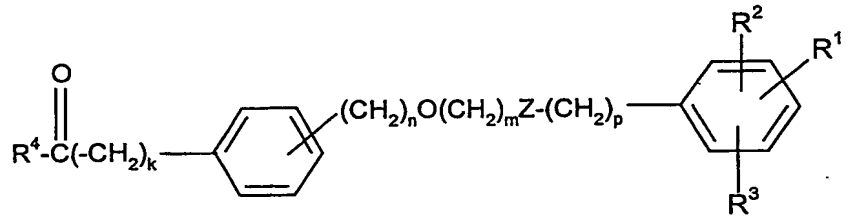
According to a further process (d) a compound of formula (I) wherein one of R^4 and R^5 represents alkyl may be prepared by reacting a compound of formula (X):



(X)

as hereinbefore defined,

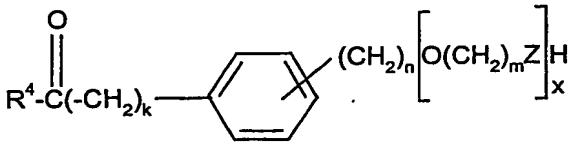
with a compound of formula (XIV):



(XIV)

under conditions suitable to effect reductive amination, for example in the presence of a reducing agent such as a borohydride, typically tetramethylammonium (triacetoxy) borohydride.

A compound of formula (XIV) may be prepared by alkylation of a compound of formula (XV)



(XV)

wherein x is zero or 1, with a compound of formula (VI) as hereinbefore defined using methods analogous to those described hereinbefore for the preparation of compounds of formula (IV).

Compounds of formula (XV) wherein x is zero are commerically available or may readily be prepared by conventional methods. Compounds of formula (XV) where x is 1 may be prepared from a corresponding compound wherein x is zero by appropriate alkylation.

It will be appreciated that at any convenient stage in the preparation of a compound of formula (I) one or more of the substituents R^1, R^2 and R^3 may, if appropriate, be converted

into a different substituent. Conveniently such conversion may be effected on a compound of formula (IV) prior to the deprotection stages.

Thus for example a compound wherein R^1 represents $-NH_2$ may be converted into a compound wherein R^1 represents XN $R^6C(O)N$ R^7 R^8 by reaction with an appropriate isocyanate or into a compound wherein R^1 represents L-XN $R^6(CO)N(CO)N$ R^7 R^8 using excess isocyanate – similarly, amide and sulfonamide derivatives may be formed by reaction with an appropriate acyl or sulfonyl chloride or anhydride. Alternatively a simple amide substituent may be prepared from the corresponding nitrile, by treatment with a base such as potassium trimethylsilanolate. Other transformations will be apparent to those skilled in the art, and may be effected by conventional reactions.

It will be appreciated that in any of the routes (a) to (d) described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral intermediates by the methods described above.

Optional conversions of a compound of formula (I), to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I), to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I), for example compounds of general formula (III) and (IV).

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

Throughout the examples, the following abbreviations are used:
LCMS: Liquid Chromatography Mass Spectrometry
HPLC: High Performance Liquid Chromatography
RT: retention time
DCM: dichloromethane
EtOAc: ethyl acetate
EtOH: ethanol
DMAP: N,N-Dimethylaminopyridine
DMF: N,N-Dimethylformamide
MeOH: methanol
THF: tetrahydrofuran
TSP+ve: thermospray mass spectrum positive mode
h: hour(s)
min: minute(s)
All temperatures are given in degrees centigrade.
Flash silica gel refers to Merck Art No. 9385; silica gel refers to Merck Art No. 7734
Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.
Solid Phase Extraction (SPE) columns are pre-packed cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.
SCX cartridges are Ion Exchange SPE columns where the stationary phase is polymeric benzene sulfonic acid. These are used to isolate amines.

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3cm x 4.6mm ID) eluting with 0.1% HCO_2H and 0.01M ammonium acetate in water (solvent A) and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0.0-7min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5min 0%B at a flow rate of 3mL/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Thermospray mass spectra were obtained on an HP 5989A spectrometer using the positive mode.

Example 1

4-((1*R*)-2-{[2-(3-{[2-(Benzyloxy)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

i) 2-[2-(3-Bromophenyl)ethoxy]tetrahydro-2*H*-pyran

p-Toluenesulphonic acid monohydrate (0.40g) was added to a stirred solution of 2-(3-bromophenyl)ethanol (5.471g) and dihydropyran (4.58g) in CH_2Cl_2 (100ml) at 0°C. The cooling bath was removed and the reaction mixture stirred at 20°C for 4 h. Et_3N (2ml) was added and the mixture evaporated under reduced pressure. The residue was purified by chromatography on a Biotage (90g) eluting with cyclohexane-Et_2O (15:1) to give the *title compound* (5.12g), ES+ve 302 / 304 $(M+NH_4)^+$

ii) {3-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]phenyl}methanol

A solution of n-butyl lithium in hexanes (9.5ml, 1.6M) was added dropwise to a stirred solution of 2-[2-(3-Bromophenyl)ethoxy]tetrahydro-2*H*-pyran (2.5g) in THF (40ml) at -70°C. After 0.5h DMF (1.1ml) was added and the reaction allowed to warm to 20°over 2h. Water (5ml) was added and mixture partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O (x2). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The resiude was dissolved in MeOH (40ml) at 0°C and treated with sodium borohydride (0.40g). After stirring at 20°C for 2.5h the reaction was recooled to 0°C and quenched by the dropwise addition of aqueous hydrochloric acid (1M). The mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography on a Biotage (40g) eluting with cyclohexane then cyclohexane-EtOAc (9:1 to 4:1) to give the *title compound* (1.30g), ES+ve 237 $(M+H)^+$

iii) 2-[2-(3-{[2-(Benzyloxy)ethoxy]methyl}phenyl)ethoxy]tetrahydro-2*H*-pyran

A solution of {3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]phenyl}methanol (0.42g) in DMF (2ml) was added dropwise to a stirred suspension of sodium hydride (0.13g, 60% in oil) in DMF (2ml) at 0°C under an atmosphere of nitrogen. After 0.3 h a solution of benzyl 2-bromoethyl ether (0.76g) in DMF (2ml) was added dropwise. The reaction mixture was allowed to warm to 20°C and stirred overnight. Water (30ml) was added to the reaction mixture and the mixture extracted with Et_2O (2 x 30ml). The combined organic extracts

were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography on a Biotage (40g) eluting with cyclohexane-Et_2O(3:1) to give the *title compound* (0.43g), ES+ve 388 $(M+NH_4)^+$

iv) 1-{[2-(Benzyloxy)ethoxy]methyl}-3-(2-bromoethyl)benzene

Triphenylphosphine dibromide (0.83g) was added portionwise to a stirred solution of 2-[2-(3-{[2-(benzyloxy)ethoxy]methyl}phenyl)ethoxy]tetrahydro-2*H*-pyran (0.39g) in CH_2Cl_2 (10ml) at 20°C. After 1.7 h the reaction was evaporated under reduced pressure and the residue suspended in cyclohexane (10ml). The mixture was filtered and the residue washed with cyclohexane. The filtrate was evaporated under reduced pressure and the residue purified by chromatography on a silica SPE cartridge (10g) eluting with cyclohexane (30ml), CH_2Cl_2 (2 x 30ml) and Et_2O (30ml). Appropriate fractions were combined and evaporated to give the *title compound* (0.35g) ES+ve 366/368 $(M+NH_4)^+$

v) (1*R*)-2-{[2-(3-{[2-(Benzyloxy)ethoxy]methyl}phenyl)ethyl]amino}-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

(1R)-2-Amino-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (0.20g) was added to a stirred solution of 1-{[2-(benzyloxy)ethoxy]methyl}-3-(2-bromoethyl)benzene (0.162g) in anhydrous DMF (2ml). The reaction mixture was stirred at 20°C for 18h then evaporated under reduced pressure. The residue was partitioned between EtOAc (20ml) and water (20ml). The aqueous phase was extracted with EtOAc (20ml) and the combined organic phases washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography on a Biotage (8g) eluting with CH_2Cl_2-MeOH-2M NH_3 in MeOH 150:8:1 to 75:8:1 to give the *title compound* (0.13g), ES+ve 492 $(MH)^+$

vi) 4-((1*R*)-2-{[2-(3-{[2-(Benzyloxy)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

A solution of (1*R*)-2-{[2-(3-{[2-(benzyloxy)ethoxy]methyl}phenyl)ethyl]amino}-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (0.12g) in glacial acetic acid (2ml) and water (1ml) was heated at 80°C for 0.5 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by chromatography on a Biotage (8g) eluting with CH_2Cl_2-MeOH-2M NH_3 in MeOH 75:8:1 to 50:8:1 to give the free base of the *title compound*. This was converted to the acetate salt using acetic acid to give the *title compound* (0.06g). LCMS RT=2.44min. ES+ve 452 $(MH)^+$

Example 2

4-{(1*R*)-2-[(2-{3-[(Benzyloxy)methyl]phenyl}ethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate

i) 2-(2-{3-[(Benzyloxy)methyl]phenyl}ethoxy)tetrahydro-2*H*-pyran

Prepared using methods similar to those in Example 1 iii) ES+ve 344 $(M+NH_4)^+$

ii) 1-[(Benzyloxy)methyl]-3-(2-bromoethyl)benzene

Prepared using methods similar to those in Example 1 iv) ES+ve 322/324 $(M+NH_4)^+$

iii) (1*R*)-2-[(2-{3-[(Benzyloxy)methyl]phenyl}ethyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

Prepared using methods similar to those in Example 1 v) ES+ve 448 $(MH)^+$

iv) 4-{(1*R*)-2-[(2-{3-[(Benzyloxy)methyl]phenyl}ethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate

Prepared using methods similar to those in Example 1 vi) LCMS RT=2.42min. ES+ve 408 $(MH)^+$

Example 3

2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{3-[(3-phenylpropoxy)methyl]phenyl}ethyl)amino]ethyl}phenol acetate

i) 2-(2-{3-[(3-Phenylpropoxy)methyl]phenyl}ethoxy)tetrahydro-2*H*-pyran

Prepared using methods similar to those in Example 1 iii) ES+ve 372 $(M+NH_4)^+$

ii) 1-(2-Bromoethyl)-3-[(3-phenylpropoxy)methyl]benzene

Prepared using methods similar to those in Example 1 iv) TSP+ve 350/352 $(M+NH_4)^+$

iii) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(2-{3-[(3-phenylpropoxy)methyl]phenyl}ethyl)amino]ethanol

Prepared using methods similar to those in Example 1 v) ES+ve 476 $(MH)^+$

iv) 2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{3-[(3-phenylpropoxy)methyl]phenyl}ethyl)amino]ethyl}phenol acetate

Prepared using methods similar to those in Example 1 vi) LCMS RT=2.58min. ES+ve 436 $(MH)^+$

Example 4

2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{3-[(4-phenylbutoxy)methyl]phenyl}ethyl)amino]ethyl}phenol acetate

i) 2-(2-{3-[(4-Phenylbutoxy)methyl]phenyl}ethoxy)tetrahydro-2*H*-pyran

Prepared using methods similar to those in Example 1 iii) TSP+ve 386 $(MH)^+$

ii) 1-(2-Bromoethyl)-3-[(4-phenylbutoxy)methyl]benzene

Prepared using methods similar to those in Example 1 iv) TSP+ve 364/366 $(M+NH_4)^+$

iii) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(2-{3-[(4-phenylbutoxy)methyl]phenyl}ethyl)amino]ethanol

Prepared using methods similar to those in Example 1 v) LCMS RT=2.44min. ES+ve 490 $(MH)^+$

iv) 2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{3-[(4-phenylbutoxy)methyl]phenyl}ethyl)amino]ethyl}phenol acetate

Prepared using methods similar to those in Example 1 vi) LCMS RT=2.69 min. ES+ve 450 $(MH)^+$

Example 5

4-((1*R*)-2-{[2-(3-{[3-(Benzyloxy)propoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

i) 2-[2-(3-{[3-(Benzyloxy)propoxy]methyl}phenyl)ethoxy]tetrahydro-2*H*-pyran

Prepared using methods similar to those in Example 1 iii) ES+ve 402 $(M+NH_4)^+$

ii) 1-{[3-(Benzyloxy)propoxy]methyl}-3-(2-bromoethyl)benzene

Prepared using methods similar to those in Example 1 iv) ES+ve 380/382 $(M+NH_4)^+$

iii) (1*R*)-2-{[2-(3-{[3-(Benzyloxy)propoxy]methyl}phenyl)ethyl]amino}-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol
Prepared using methods similar to those in Example 1 v) ES+ve 506 $(MH)^+$

iv) 4-((1*R*)-2-{[2-(3-{[3-(Benzyloxy)propoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate
Prepared using methods similar to those in Example 1 vi) LCMS RT=2.44min. ES+ve 466 $(MH)^+$

Example 6
4-((1*R*)-2-{[2-(4-{[2-(Benzyloxy)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

i) {4-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]phenyl}methanol
Prepared using methods similar to those in Example 1 ii) TSP+ve 254 $(M+NH_4)^+$

ii) 2-[2-(4-{[2-(Benzyloxy)ethoxy]methyl}phenyl)ethoxy]tetrahydro-2*H*-pyran
Prepared using methods similar to those in Example 1 iii) TSP+ve 388 $(M+NH_4)^+$

iii) 1-{[2-(Benzyloxy)ethoxy]methyl}-4-(2-bromoethyl)benzene
Prepared using methods similar to those in Example 1 iv) TSP+ve 352/354 $(M+NH_4)^+$

iv) (1*R*)-2-{[2-(4-{[2-(Benzyloxy)ethoxy]methyl}phenyl)ethyl]amino}-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol
Prepared using methods similar to those in Example 1 v) ES+ve 492 $(MH)^+$

v) 4-((1*R*)-2-{[2-(4-{[2-(Benzyloxy)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate
Prepared using methods similar to those in Example 1 vi) LCMS RT=2.43min. ES+ve 452 $(MH)^+$

Example 7
2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{3-[(2-phenylethoxy)methyl]phenyl}ethyl)amino]ethyl}phenol acetate

i) 3-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]benzyl methanesulfonate

Methanesulfonyl chloride (0.3ml) was added slowly to a stirred solution of {3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]phenyl}methanol (0.71g) and Et_3N (0.63ml) in CH_2Cl_2 (4ml) at 0°C. The reaction was allowed to warm to r.t. and stirred for 1h. Water and CH_2Cl_2 were added and the phases separated using an International Sorbent Technology Phase Separator cartridge. The aqueous phase was extracted with additional CH_2Cl_2 and the combined organic phases were evaporated under reduced pressure. The residue purified by chromatography on a silica SPE cartridge (10g) eluting with cyclohexane-ethyl acetate (100:0 to 0:100 in a stepped gradient) to give the *title compound* (0.79g). ES+ve 332 $(M+NH_4)^+$

ii) 2-(2-{3-[(2-Phenylethoxy)methyl]phenyl}ethoxy)tetrahydro-2*H*-pyran

2-(2-Hydroxyethyl)benzene (0.119ml) was added slowly to a stirred suspension of sodium hydride (0.06g, 60% diposersion in oil) in DMF (2ml) at 0°C under an atmosphere of nitrogen. The reaction was stirred for 0.5h then a solution of 3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]benzyl methanesulfonate (0.47g) in DMF (1.5ml) was added. The reaction stirred for 2h then quenched by the dropwise addition of water. The mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic phases evaporated under reduced pressure. The residues was purified by chromatography on a silica SPE cartridge (10g) eluting with cyclohexane-EtOAc (19:1) to give the title compound (0.31g). ES+ve 358 $(M+NH_4)^+$

iii) 1-(2-Bromoethyl)-3-[(2-phenylethoxy)methyl]benzene

Carbon tetrabromide (0.42g) was added to a stirred solution of 2-(2-{3-[(2-phenylethoxy)methyl]phenyl}ethoxy)tetrahydro-2*H*-pyran (0.31g) in CH_2Cl_2 (4ml) at <5°C. Triphenylphosphine (0.66g) was added portionwise then the reaction mixture allowed to warm to 20 °C and stirred for 18h. The solvent was removed by evaporation and the residue chromatographed on an SPE cartridge (10g) eluting with cyclohexane-CH_2Cl_2 (9:1 to 7:3) to give the *title compound* (0.256g). ES+ve 338 $(M+NH_4)^+$

iv) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(2-{3-[(2-phenylethoxy)methyl]phenyl}ethyl)amino]ethanol

Prepared using methods similar to those in Example 1 ii) ES+ve 462 $(MH)^+$

v) 2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(2-{3-[(2-phenylethoxy)methyl]phenyl}ethyl)amino]ethyl}phenol acetate

Prepared using methods similar to those in Example 1 iii) LCMS RT=2.43min. ES+ve 452 $(MH)^+$

Example 8

4-((1*R*)-2-{[2-(3-{[(2,6-Dichlorobenzyl)oxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

i) 2-[2-(3-{[(2,6-Dichlorobenzyl)oxy]methyl}phenyl)ethoxy]tetrahydro-2*H*-pyran
Prepared using methods similar to those in Example 1 iii) ES+ve 412 / 414 / 416 $(M+NH_4)^+$

ii) 2-({[3-(2-Bromoethyl)benzyl]oxy}methyl)-1,3-dichlorobenzene
Prepared using methods similar to those in Example 7 iii) ES+ve 390 / 392 / 394 / 396 $(M+NH_4)^+$

iii) (1*R*)-2-{[2-(3-{[(2,6-Dichlorobenzyl)oxy]methyl}phenyl)ethyl]amino}-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol
Prepared using methods similar to those in Example 1 v) ES+ve 516 / 518 / 520 $(MH)^+$

iv) 4-((1*R*)-2-{[2-(3-{[(2,6-Dichlorobenzyl)oxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate
Prepared using methods similar to those in Example 1 vi) LCMS RT=2.58min. ES+ve 476/ / 478 / 480 $(MH)^+$

Example 9

4-((1*R*)-2-{[2-(3-{[2-(2,3-dihydro-1-benzofuran-4-yl)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

i) 4-[2-({3-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]benzyl}oxy)ethyl]-2,3-dihydro-1-benzofuran
Prepared using methods similar to those in Example 7 ii) ES+ve 400 $(M+NH_4)^+$

ii) 4-(2-{[3-(2-Bromoethyl)benzyl]oxy}ethyl)-2,3-dihydro-1-benzofuran
Prepared using methods similar to those in Example 7 iii) ES+ve 378 / 380 $(M+NH_4)^+$

iii) 4-((1*R*)-2-{[2-(3-{[2-(2,3-Dihydro-1-benzofuran-4-yl)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

(1R)-2-Amino-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (0.26g) was added to a stirred solution of 4-(2-{[3-(2-bromoethyl)benzyl]oxy}ethyl)-2,3-dihydro-1-benzofuran (0.21g) in anhydrous DMF (3ml). The reaction mixture was stirred at 60 C for 4h then evaporated under reduced pressure. The residue was applied to a C-18 reverse phase SPE cartridge and eluted with acetonitrile -water-formic acid (3:96:1 followed by 15:84:1 then 55:44:1). Formic acid (2ml) was added to the fractions eluted with acetonitrile-water-formic acid (55:44:1) and the solvent removed by evaporation. The residue was purified by chromatography on a silica SPE cartridge (10g) eluting with CH_2Cl_2-2M NH_3 in MeOH (96:4 to 9:1) to give the free base of the *title compound*. This was converted to the acetate salt using acetic acid to give the *title compound* (0.19g). LCMS RT=2.50min. ES+ve 464 $(MH)^+$

Example 10

4-((1*R*)-1-Hydroxy-2-{[2-(3-{[2-(2-methoxyphenyl)ethoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol acetate

i) 2-[2-(3-{[2-(2-Methoxyphenyl)ethoxy]methyl}phenyl)ethoxy]tetrahydro-2*H*-pyran

Prepared using methods similar to those in Example 7 ii) ES+ve 388 $(M+NH_4)^+$

ii) 1-(2-{[3-(2-Bromoethyl)benzyl]oxy}ethyl)-2-methoxybenzene

Prepared using methods similar to those in Example 7 iii) ES+ve 366 / 368 $(M+NH_4)^+$

iii) 4-((1*R*)-1-Hydroxy-2-{[2-(3-{[2-(2-methoxyphenyl)ethoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol acetate

Prepared using methods similar to those in Example 9 iii) LCMS RT=2.58min. ES+ve 451 $(MH)^+$

Example 11

4-((1*R*)-1-Hydroxy-2-{[2-(3-{[2-(3-methoxyphenyl)ethoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol acetate

i) 2-[2-(3-{[2-(3-Methoxyphenyl)ethoxy]methyl}phenyl)ethoxy]tetrahydro-2*H*-pyran

Prepared using methods similar to those in Example 7 ii) ES+ve 388 $(M+NH_4)^+$

ii) 1-(2-Bromoethyl)-3-{[2-(3-methoxyphenyl)ethoxy]methyl}benzene
Prepared using methods similar to those in Example 7 iii) ES+ve 366 / 368 $(M+NH_4)^+$

iii) 4-((1*R*)-1-Hydroxy-2-{[2-(3-{[2-(3-methoxyphenyl)ethoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol acetate
Prepared using methods similar to those in Example 9 iii) LCMS RT=2.51min. ES+ve 464 $(MH)^+$

Example 12
4-((1*R*)-1-Hydroxy-2-{[2-(3-{[2-(4-methoxyphenyl)ethoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol acetate

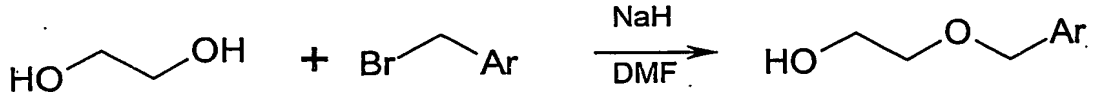
i) 2-[2-(3-{[2-(4-Methoxyphenyl)ethoxy]methyl}phenyl)ethoxy]tetrahydro-2*H*-pyran
Prepared using methods similar to those in Example 7 ii) ES+ve 388 $(M+NH_4)^+$

ii) 1-(2-Bromoethyl)-3-{[2-(4-methoxyphenyl)ethoxy]methyl}benzene
Prepared using methods similar to those in Example 7 iii) ES+ve 366 / 368 $(M+NH_4)^+$

iii) 4-((1*R*)-1-Hydroxy-2-{[2-(3-{[2-(4-methoxyphenyl)ethoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol acetate
Prepared using methods similar to those in Example 9 iii) LCMS RT=2.50min. ES+ve 451 $(MH)^+$

Intermediates 1-39
Intermediates 1-39 (used in the preparation of examples 13-67) were prepared by one of the general methods A-E shown below, both schematically and by a representative example.

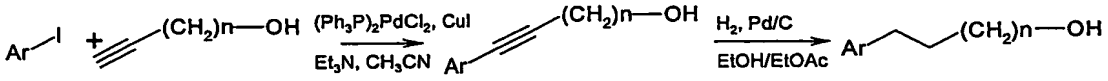
General Method A



Intermediate 1
i) 3-[(2-Hydroxyethoxy)methyl]benzonitrile

Ethylene glycol (6.2g) was treated with sodium hydride (60% dispersion in oil, 480mg) and stirred for 30 min. 3-(Bromomethyl)benzonitrile (1.96g) was added and the reaction mixture heated at 80°C for 15 h. The reaction mixture was cooled to room temperature and quenched with water. The resultant mixture was partitioned between water and ether. The aqueous phase was extracted with ether and the combined organic phase dried and concentrated *in vacuo*. The residue was purified by chromatography (SPE, eluted with gradient between cyclohexane and 50% EtOAc in cyclohexane) to give *the title compound* (780mg). LCMS RT= 2.22 min.

General Method B



Intermediate 2

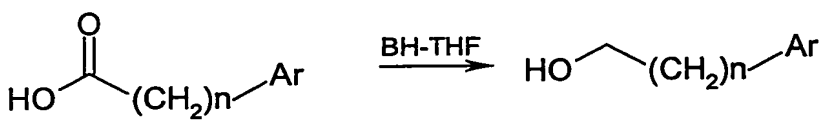
i) 3-(4-Hydroxybut-1-ynyl)phenyl acetate

A solution of 3-iodophenyl acetate (5.6g) (J. Org. Chem. 1983, 48, 1542-4) in acetonitrile (100mL) was treated triethylamine (8mL), $(Ph_3P)_2PdCl_2$ (673mg) and CuI (368mg) and stirred at room temperature. 3-Butyn-1-ol (1.78g) was added and the reaction mixture stirred for a further 20 h and concentrated *in vacuo*. The residue was purified by chromatography (SPE, gradient from cyclohexane to DCM) to give the *title compound*. (4.47g) LCMS RT= 2.54 min

ii) 3-(4-Hydroxybutyl)phenyl acetate

5% Pd on Carbon (50%, wet) under nitrogen was treated with a solution of 3-(4-hydroxybut-1-ynyl)phenyl acetate (4.47g) in ethyl acetate (100mL) and ethanol (100mL). The reaction mixture was flushed with nitrogen and stirred under hydrogen for 20 h. The reaction mixture was flushed with nitrogen and filtered through celite under nitrogen. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography (SPE, gradient from cyclohexane to EtOAc) to give the *title compound*. (3.81g) LCMS RT= 2.64

General Method C

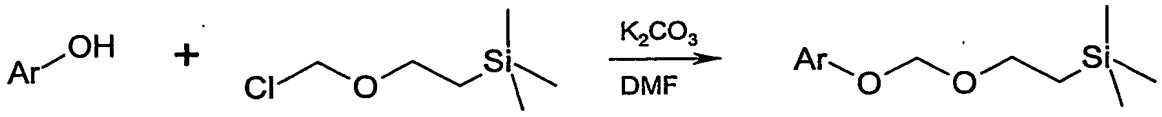


Intermediate 3

i) 3-[4-(Methylsulfonyl)phenyl]propan-1-ol

A solution of 3-[4-(methylsulfonyl)phenyl]propanoic acid (600mg) in dry THF (10mL) was treated with borane-THF (1M in THF, 4.96mL) and the resultant solution stirred at room temperature for 2 h. The reaction mixture was quenched with water and partitioned between EtOAc and water. The organic phase was washed with 2N NaOH and dried ($MgSO_4$) . The organic solution was concentrated *in vacuo* to give the *title compound.* (482mg) LCMS RT= 2.02min

General Method D

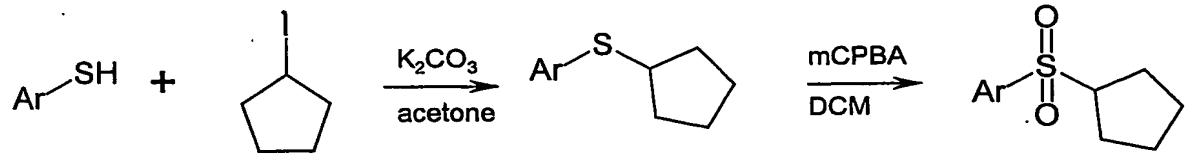


Intermediate 4

i) 2-(2-{[2-(Trimethylsilyl)ethoxy]methoxy}phenyl)ethanol

A solution of 2-(2-hydroxyphenyl)ethanol (69 mg) in dry DMF (10mL) was treated with potassium carbonate (86mg) under nitrogen. 2-(trimethylsilyl)ethoxymethy chloride (110 µL) was added and the reaction mixtures stirred at room temperature for 16 h prior to partitioning between EtOAc and water. The organic phase was washed with sat. $NH_4Cl_{(aq)}$, water and dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by chromatography (SPE, gradient from cyclohexane to EtOAc) to give the *title compound.* (49mg) LCMS RT= 3.59 min

General Method E



Intermediate 5

i) 4-Bromophenyl cyclopentyl sulphide

To a stirred solution of 4-bromobenzenethiol (5.00g) in N,N-dimethylformamide (100mL) was added cyclopentyl bromide (6.34g) and potassium carbonate (9.27g). The mixture was allowed to stir at room temperature under nitrogen for 67h. The reaction mixture was partitioned between 2N HCl and ethyl acetate. The organic phase was washed with brine

and dried ($MgSO_4$). Filtration and removal of the solvent under reduced pressure gave *the title compound* (5.88g). LCMS =4.28 min.

ii) 4-Bromophenyl cyclopentyl sulfone

A stirred solution of 4-bromophenyl cyclopentyl sulphide (4.00g) in dichloromethane (200ml) under nitrogen was treated with *meta*-chloroperbenzoic acid (9.42g, assuming 57%), and stirred at room temperature for 2h. The reaction mixture was poured into water and washed with sodium sulphite solution (15%) until no peroxide remained. The organic phase was washed with brine and dried ($MgSO_4$). Filtration and removal of the solvent under reduced pressure gave *the title compound* (3.91g). LCMS RT = 3.15 min.

The following intermediates were prepared according to the general methods A-E above.

Intermediate No.	Name	General Method	Inter-mediate	LCMS RT
6	3-[(2-Hydroxyethoxy)methyl]benzonitrile	General Method A		2.22 min
7	2-[(2,6-Dichlorobenzyl)oxy]ethanol	General Method A		2.64 min
8	2-[(3-Fluorobenzyl)oxy]ethanol	General Method A		2.37 min
9	2-[(3,5-Dimethylbenzyl)oxy]ethanol	General Method A		2.79 min
10	2-[(3-Methoxybenzyl)oxy]ethanol	General Method A		2.34 min
11	2-{[3-(Trifluoromethoxy)benzyl]oxy}ethanol	General Method A		2.93 min
12	3-(4-Hydroxybutyl)phenyl acetate	General Method B	2.54 min	2.64 min
13	3-(4-Hydroxybutyl)benzenesulfonamide	General Method B	2.16 min	2.14 min
14	4-(3-Hydroxypropyl)benzonitrile	General Method B	2.39 min	2.38 min
15	4-(4-Hydroxybutyl)benzonitrile	General Method B	2.52 min	2.56 min

16	3-(3-Hydroxypropyl)benzonitrile	General Method B	2.36 min	2.42 min
17	3-[4-(Methylsulfonyl)phenyl]propan-1-ol	General Method C		2.02 min
18	[4-(Methylsulfonyl)phenyl]methanol	General Method C		1.56 min
19	2-(2-{[2-(Trimethylsilyl)ethoxy]methoxy}phenyl)ethanol	General Method D		3.59 min
20	(3-{[2-(Trimethylsilyl)ethoxy]methoxy}phenyl)methanol	General Method D		3.51 min
21	(4-{[2-(Trimethylsilyl)ethoxy]methoxy}phenyl)methanol	General Method D		3.43 min
22	3-(2-{[2-(Trimethylsilyl)ethoxy]methoxy}phenyl)propan-1-ol	General Method C & D	2.20 min	3.61 min
23	3-(3-{[2-(Trimethylsilyl)ethoxy]methoxy}phenyl)propan-1-ol	General Method C & D	2.09 min	3.67 min
24	4-[4-(Cyclopentylsulfonyl)phenyl]butan-1-ol	General Methods E & B	2.74 min	2.64 min
25	3-[4-(Cyclopentylsulfonyl)phenyl]propan-1-ol	General Methods E & B	2.67 min	2.79 min

Intermediate 26

2-[(3-{[2-(Trimethylsilyl)ethoxy]methoxy}benzyl)oxy]ethanol

i) 3-{[2-(Trimethylsilyl)ethoxy]methoxy}benzyl bromide

A solution of (3-{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)methanol (4g) in dry DCM (50 mL) was cooled to 0°C and treated with DIPEA (4.08mL). Methane sulphonyl chloride (1.46 mL) was added dropwise and the reaction mixture stirred at 0°C for 2 h prior to

diluting with DCM and washing with sat. $NaHCO_{3\,(aq)}$. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was redissolved in acetonitrile (50mL) and treated with tetra-n-butyl ammonium bromide (9.9g) and the reaction mixture heated at 50°C for 2.5 h and room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography (SPE, gradient from cyclohexane to 25% Et_2O) to give the *title compound.* (2.43g) LCMS RT= 4.02 min

ii) 2-[(3-{[2-(Trimethylsilyl)ethoxy]methoxy}benzyl)oxy]ethanol
Prepared similarly to General Method A. LCMS RT = 3.33 min

Intermediate 27
4-(6-Methoxypyrazin-2-yl)butan-1-ol

i) 2,6-diiodopyrazine
A solution of 2,6-dichloropyrazine (4g) in hydroiodic acid (47%) was stirred vigorously for 24 hr. The reaction mixture was poured into water (200mL) and extracted with DCM. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and EtOAc) to give the title compound. LCMS RT= 2.86 min.

ii) 2-Iodo-6-methoxypyrazine
A solution of 2,6,diiodopyrazine (4g) in dry DMF (80mL) was treated with sodium methoxide (777mg) and the reaction mixture stirred for 18hrs. A further portion of sodium methoxide was added and the reaction mixture stirred for a further 4 h. The reaction mixture was poured onto water and extracted with EtOAc. The organic phase was washed with sat. $NH_4Cl_{(aq)}$, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and DCM) to give the title compound. LCMS RT= 2.69 min.

iii) 4-(6-Methoxypyrazin-2-yl)but-3-yn-1-ol
Prepared similarly to General Method B part i. LCMS RT = 2.07 min

iv) 4-(6-Methoxypyrazin-2-yl)butan-1-ol
Prepared similarly to General Method B part ii. LCMS RT = 2.12 min

Intermediate 28

2-{[3-(Cyclopentylsulfonyl)benzyl]oxy}ethanol

i) 1-(Hydroxymethyl)-3-(cyclopentylthio)benzene

A solution of 3-iodobenzyl alcohol (5g) in dry N-methylpyrollidinone (50 mL) was treated with triethylamine (20mL), 1,1'-bis(diphenylphosphine)ferrocene (710mg) and tris(dibenzylidineacetone) dipalladium (0) (285mg). The reaction mixture was degassed and flushed thoroughly with nitrogen. Cyclopentyl mercaptan (2.3 mL) was added and the reaction mixture heated at 70°C for 5 h and room temperature for a further 16 h. The reaction mixture was poured onto water and extracted into EtOAc. The organic phase was washed with sat. Na_2CO_3, 2N HCl and water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and cyclohexane/EtOAc 1:1) to give the *title compound*. (4.62g) LCMS RT= 3.23 min.

ii) 1-(Bromomethyl)-3-(cyclopentylthio)benzene

A solution of 1-(hydroxymethyl)-3-(cyclopentylthio)benzene (4.6g) in dry DCM (100mL) was treated with triphenylphosphine (14.5g) and protionwise with CBr_4 (18.4g). The reaction mixture was stirred at room temperature for 3 h prior to partitioning between EtOAc and water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and cyclohexane/EtOAc 1:1) to give the *title compound*. (1.1g) LCMS RT= 3.98 min.

iii) 2-{[3-(Cyclopentylthio)benzyl]oxy}ethanol

Prepared similarly to General Method A. LCMS RT = 3.17 min

Intermediate 29

i) 2-{[3-(Cyclopentylsulfinyl)benzyl]oxy}ethanol

A solution of 2-{[3-(cyclopentylthio)benzyl]oxy}ethanol (520mg) in ethanol (15mL) was treated with a solution of $NaIO_4$ (1.77g) in water (5mL). The resultant solution was stirred at room temperature for 2 h prior to concentration in vacuo. The residue was partitioned between water and EtOAc, the organic phase washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and cyclohexane/EtOAc, 1:1) to give the *title compound*. (201mg) LCMS RT= 2.40 min.

ii) 2-{[3-(Cyclopentylsulfonyl)benzyl]oxy}ethanol

A solution of 2-{[3-(cyclopentylsulfinyl)benzyl]oxy}ethanol (200mg) in dry DCM (10mL) was cooled to 0°C and treated with m-chloro-perbenzoic acid (246mg). The reaction was stirred at room temperature for 0.5h and room temperature for 2 h. The reaction mixture was partitioned between DCM and sat. sodium sulphite solution. The organic phase was washed with sat. sodium sulphite solution, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography (SPE, Gradient between cyclohexane and cyclohexane/EtOAc, 1:1) to give the *title compound.* (436mg) LCMS RT= 2.55 min.

Intermediate 30

[3-(Cyclopentylsulfonyl)phenyl]methanol

A solution of 1-(hydroxymethyl)-3-(cyclopentylthio)benzene (4.3g) in dry DCM (300mL) was cooled to 0°C and treated with m-chloro-perbenzoic acid (15.6g). The reaction mixture was stirred at room temperature for 2 h and room temperature for 16 h. The reaction mixture was partitioned between DCM and sat. sodium sulphite solution. The organic phase was washed with sat. sodium sulphite solution, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and EtOAc) to give the *title compound.* (4.52g) LCMS RT= 2.43 min.

Intermediate 31

4-[3-(Cyclopentylsulfinyl)phenyl]butan-1-ol

i) [4-(3-Bromophenyl)butoxy](*tert*-butyl)diphenylsilane

A solution of 4-(3-bromophenyl)butan-1-ol (5g) [WO 0266422 A1] in dry DMF (50mL) was treated with imidazole (1.8g) and tert-butyldiphenylsilyl chloride (7.2g) and stirred at room temperature for 16 h. The reaction mixture was partitioned between water and EtOAc. The organic phase was washed with 2N HCl, water, sat. $NH_4Cl_{(aq)}$, water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and cyclohexane/EtOAc 5:1) to give the *title compound.* (9.67g) LCMS RT= 4.82 min

ii) *tert*-Butyl{4-[3-(cyclopentylthio)phenyl]butoxy}diphenylsilane

A solution [4-(3-bromophenyl)butoxy](*tert*-butyl)diphenylsilane (2g) in dry N-methylpyrollidine (15mL) was treated with triethylamine (4mL), 1,1'-bis(diphenylphosphine)ferrocene (284mg) and tris(dibenzylidineacetone) dipalladium (0)

(114mg). The reaction mixture was degassed and flushed thoroughly with nitrogen. Cyclopentyl mercaptan (436mg) was added and the reaction mixture heated at 70°C for 3 h and room temperature for a further 16 h. The reaction mixture was poured onto water and extracted into EtOAc. The organic phase was washed with sat. Na_2CO_3, 2N HCl and water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and cyclohexane/DCM 5:1) to give the *title compound*. (1.48g) LCMS RT= 4.94 min.

iii) *tert*-Butyl{4-[3-(cyclopentylsulfinyl)phenyl]butoxy}diphenylsilane

A solution of *tert*-butyl{4-[3-(cyclopentylthio)phenyl]butoxy}diphenylsilane (1.48g) in ethanol (50mL) was treated with a solution of $NaIO_4$ (2.6g) in water (16mL). The resultant solution was stirred at room temperature for 3 h prior to concentration *in vacuo*. The residue was partitioned between water and EtOAc, the organic phase washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and EtOAc) to give the *title compound*. (690mg) LCMS RT= 4.45 min.

iv) 4-[3-(Cyclopentylsulfinyl)phenyl]butan-1-ol

A solution of *tert*-butyl{4-[3-(cyclopentylsulfinyl)phenyl]butoxy}diphenylsilane (690mg) in dry THF (10mL) was treated with a solution of tetra-n-butylammonium fluoride (3mL, 1M in THF) and the resultant reaction mixture stirred at room temperature for 5 h prior to concentration *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and EtOAc) to give the *title compound*. (362mg) LCMS RT= 2.64 min.

Intermediate 32

(5*R*)-3-{2-[3-(Bromomethyl)phenyl]ethyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

i) 3-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]benzyl acetate

A solution of {3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]phenyl}methanol (36.8g) in DCM (200mL) was cooled to 0°C and treated with pyridine (14mL) . Acetic anhydride (13mL) was added dropwise. The resultant mixture was stirred at room temperature, under nitrogen, for 16 h. The reaction mixture was partitioned between DCM (100mL) and 2N hydrochloric acid (100mL). The organic phase was washed with 2N hydrochloric acid (100mL), 2N sodium bicarbonate solution (100mL) and water (200mL), dried (Na_2SO_4)

and evaporated under reduced pressure. This was chromatographed on a Biotage cartridge (4 x 90g) eluting with cyclohexane - ethyl acetate , (3:1) to give the *title compound* (37.23g). LCMS RT = 3.10 min

ii) 3-(2-Hydroxyethyl)benzyl acetate

A solution of 3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]benzyl acetate (20g) in acetic acid (100mL) and water (20mL) was heated at 80°C for 1.5 h. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on a Biotage cartridge (2 x 90g) eluting with cyclohexane – ethyl acetate (3:1) to (1:1) to give the *title compound* (13.42g). LCMS RT = 2.30 min

iii) 3-(2-Bromoethyl)benzyl acetate

A solution of 3-(2-hydroxyethyl)benzyl acetate (13.01g) in DCM (100mL) was cooled to 0°C and treated with N,N-diisopropylethylamine (17.5mL). Mesyl chloride (6.22mL) was added and the reaction mixture stirred at 0°C for 1 h. The reaction was washed with saturated sodium bicarbonate solution (150mL). The organic phase was dried (Na_2SO_4) concentrated *in vacuo*. A solution of the residue in acetonitrile (130mL) was treated with tetrabutylammonium bromide (33g). The reaction mixture was heated at 70°C for 1.5 h before concentrating *in vacuo*. The resultant oil was partitioned between diethyl ether (150mL) and water (150mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on a Biotage cartridge (90g) eluting with cyclohexane – diethyl ether (3:1) to give the *title compound* (10.29g) LCMS RT = 3.23 min.

iv) 3-(2-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}ethyl)benzyl acetate

A solution of 3-(2-bromoethyl)benzyl acetate (8.08g) in anhydrous DMF (100mL) was treated with (1*R*)-2-amino-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (WO02/70490) (10.4g) and N,N-diisopropylethylamine (8.1mL). The reaction mixture was stirred at 50°C for 18 h then evaporated under reduced pressure. The residue was partitioned between ethyl acetate (100mL) and water (100mL). The organic layer was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on a Biotage cartridge (90g) eluting with dichloromethane – methanol (10:1) to give the *title compound* (5.4g) LCMS RT = 2.32 min.

v) 3-{2-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl acetate

A solution of 3-(2-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl] amino}ethyl)benzyl acetate (5.4g) in anhydrous THF(100mL) was treated with 1,1`-carbonyldiimidazole (4.38g) and stirred at room temperature for 4 h before concentrating *in vacuo*. The residue was partitioned between ethyl acetate (100mL) and water (100mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on a Biotage cartridge (90g) eluting with cyclohexane – ethyl acetate (2:1) to (1:1) to give the *title compound* (4.13g) LCMS RT = 3.17 min

vi) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{2-[3-(hydroxymethyl)phenyl]ethyl}-1,3- oxazolidin-2-one

To a solution of 3-{2-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl acetate (4.13g) in anhydrous THF (100mL) was added potassium trimethylsilanolate (2.5g). The reaction mixture was stirred at room temperature for 1.5 h before adding water (80mL) followed with ethyl acetate (80mL).The aqueous phase was extracted with ethyl acetate and the combined organic phases washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on a Biotage cartridge (90g) eluting with ethyl acetate – cyclohexane (2:1) to give the *title compound* (2.91g). LCMS RT = 2.94 min.

vii) (5*R*)-3-{2-[3-(Bromomethyl)phenyl]ethyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{2-[3-(hydroxymethyl) phenyl]ethyl}-1,3-oxazolidin-2-one (2.51g) in anhydrous DCM (100mL) was cooled to 0°C and treated with N,N-diisopropylethylamine (1.71mL). Mesyl chloride (1mL) was added and the reaction mixture stirred at 0°C for 1.5 h.

The reaction was washed with saturated sodium bicarbonate solution (80mL). The organic phase was dried (Na_2SO_4) concentrated *in vacuo*. A solution of the residue in acetonitrile (100mL) was treated with tetrabutylammonium bromide (3.17g). The reaction mixture was heated at 70°C for 1.5 h before concentrating *in vacuo*. The resultant oil was partitioned between diethyl ether (80mL) and water (80mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*.

The residue was chromatographed on a Biotage cartridge (90g) eluting with ethyl acetate – cyclohexane (1:1) to give the *title compound* (2.29g) LCMS RT = 3.46 min.

Intermediate 33

3-(2-Hydroxyethyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

i) Methyl [3-(aminosulfonyl)phenyl]acetate

0.880 Ammonia solution (2mL) was added to a stirred solution of methyl [3-(chlorosulfonyl)phenyl]acetate (Beecham EP91749A) (1.75g) in dichloromethane (10mL) and acetonitrile (10mL). After two hours stirring at 21° the solution was partitioned between dichloromethane and water. The aqueous layer was extracted with further dichloromethane and the combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. Dichloromethane was added and the white solid was collected by filtration to give the *title compound* (0.67g). LCMS RT= 1.97 min.

ii) Methyl {3-[(bis{[2-(trimethylsilyl)ethoxy]methyl}amino)sulfonyl]phenyl}acetate

Methyl [3-(aminosulfonyl)phenyl]acetate (0.67g) was stirred with sodium hydride (60% oil dispersion, (0.26g) in DMF (15mL) at 21° for ten minutes and then 2-(trimethylsilyl)ethoxymethyl chloride (1.04g) was added. After two hours the solution was partitioned between pH 6.4 aqueous phosphate buffer and ethyl acetate. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel in mixtures of ethyl acetate in 40-60 petroleum ether to give the *title compound* (0.72g). LCMS RT= 4.35 min.

iii) 3-(2-Hydroxyethyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

Methyl {3-[(bis{[2-(trimethylsilyl)ethoxy]methyl}amino)sulfonyl]phenyl}acetate (0.72g) was stirred in THF (10mL) under nitrogen at 21° and a solution of lithium aluminium hydride (1M in diethyl ether, 1mL) was added over 1 min. After 15 min, wet THF was added cautiously and the solution was partitioned between water and dichloromethane. The aqueous layer was extracted with more dichloromethane and the combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel in mixtures of ethyl acetate in 40-60 petroleum ether to give the *title compound* (0.38g). LCMS RT= 4.07 min.

Intermediate 34

3-(3-Hydroxypropyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

i) 3-(3-Hydroxyprop-1-ynyl)benzenesulfonamide

A solution of 3-bromobenzene-1-sulfonamide (944mg) in anhydrous tetrahydrofuran (20mL) was treated with triethylamine (10mL) and dichlorobis(triphenylphosphine)palladium(II) (117mg) and copper iodide (32mg).The solution was heated to reflux prior to addition of a solution of propyn-1-ol (187mg) in anhydrous tetrahydrofuran (5mL). The reaction mixture was heated for 16 h and then concentrated *in vacuo*. The residue was purified by chromatography (SPE, Gradient between cyclohexane and EtOAc) to give the *title compound* (196mg). LCMS RT = 1.97 min

ii) 3-(3-Hydroxypropyl)benzenesulfonamide

5% Palladium on Carbon (50%, wet) under nitrogen was treated with a solution of 3-(3-hydroxyprop-1-ynyl)benzenesulfonamide (196mg) in ethanol (10mL). The reaction mixture was flushed with nitrogen and stirred under hydrogen for 16 h. The reaction mixture was then flushed with nitrogen and filtered through celite under nitrogen. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography (SPE, gradient from cyclohexane to EtOAc) to give the *title compound* (57mg) LCMS RT = 1.90 min

iii) 3-(3-Hydroxypropyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

3-(3-Hydroxypropyl)benzenesulfonamide (54mg) was stirred with sodium hydride (60% dispersion in oil, 22mg) in DMF (5mL) at room temperature for 10 min and then 2-(trimethylsilyl)ethoxymethyl chloride (0.088mL) was added. The reaction mixture was stirred at room temperature for 18 h. The mixture was then partitioned between pH 6.4 aqueous phosphate buffer and ethyl acetate. The aqueous was extracted with EtOAc and the combined organics were washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography (SPE, eluted with cyclohexane–ethyl acetate, 2:1) to give the *title compound* (63mg) LCMS RT = 3.99 min

Intermediate 35

4-(2,6-Dichlorophenyl)butan-1-ol

i) 4-(2,6-Dichlorophenyl)but-3-yn-1-ol

A solution of 1,3-dichloro-2-iodobenzene (3.8g) in diethylamine (100mL) was treated with dichlorobis(triphenylphosphine)palladium(II) (364mg) and copper iodide (199mg) and was heated at reflux. 3-Butyn-1-ol (962mg) was added and the reaction mixture was stirred at 80°C for 16 h. The reaction mixture was then concentrated *in vacuo*. The residue was

purified by chromatography (SPE, gradient from cyclohexane to dichloromethane) to give the *title compound* (2.2g) LCMS RT = 3.06 min

ii) 4-(2,6-Dichlorophenyl)butan-1-ol

Platinum (IV) oxide (180mg) under nitrogen was treated with a solution of 4-(2,6-dichlorophenyl)but-3-yn-1-ol (1.8g) in ethanol(100mL) and ethyl acetate (100mL). The reaction mixture was flushed with nitrogen and treated with hydrogen and was stirred until the required amount of hydrogen had been consumed. The reaction mixture was flushed with nitrogen, filtered through Celite and concentrated *in vacuo.* The resultant residue was purified by chromatography (SPE, gradient from cyclohexane to ethyl acetate) to give the *title compound* (1.49g). LCMS RT = 3.22 min

Intermediate 36

N-[3-(4-Hydroxybutyl)phenyl]urea

i) 4-(3-Aminophenyl)but-3-yn-1-ol

Prepared with 3-iodoaniline and 3-butyn-1-ol using similar methods to those in Intermediate 34 i). LCMS RT = 1.74 min

ii) 4-(3-Aminophenyl)butan-1-ol

Prepared from 4-(3-aminophenyl)but-3-yn-1-ol using similar methods to those in Intermediate 35 ii). LCMS RT = 1.61 min

iii) 3-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}butyl)aniline

A stirred solution of 4-(3-aminophenyl)butan-1-ol (3.66g) in DMF (30mL), under nitrogen, was treated with imidazole (1.66g) and *tert*-butyldimethylsilyl chloride (3.5g). Stirring was continued at room temperature for 18 h. The mixture was concentrated *in vacuo* and the residue partitioned between aqueous ammonium chloride (200mL) and ethyl acetate (150mL). The aqueous layer was extracted with ethyl acetate. The combined organics were washed with water (200mL), dried (Na_2SO_4) and evaporated *in vacuo.* The residue was chromatographed on a Biotage cartridge (100g) eluting with petroleum ether – ethyl acetate, (9:1) to give the *title compound* (4.6g) LCMS RT = 3.89 min

iv) *N*-[3-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}butyl)phenyl]urea

A stirred solution of 3-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)aniline (5.16g) in anhydrous DCM (50mL), under nitrogen, was treated dropwise with a solution of trichloroacetyl

isocyanate (2.36mL) in anhydrous DCM (6mL). This was stirred at room temperature for 1 h before adding 2N sodium hydroxide solution (50mL). The resultant mixture was stirred at 70°C– 80°C for 5 h. The layers were separated and the aqueous extracted with DCM (50mL). The combined organics were evaporated *in vacuo* and the resultant residue chromatographed on a Biotage cartridge (100g) eluting with ethyl acetate – petroleum ether, (2:1) to give the *title compound* (5.71g). LCMS RT = 3.78 min

v) *N*-[3-(4-Hydroxybutyl)phenyl]urea

A stirred solution of *N*-[3-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)phenyl]urea (5.67g) in THF (50mL) was treated with trifluoroacetic acid (18.56mL). The reaction mixture was stirred at room temperature for 1 h and then allowed to stand at room temperature overnight. The reaction mixture was then concentrated *in vacuo* and the residue azeotroped with methanol. A solution of the residue in methanol (100mL) was then heated at reflux for 20 h before concentrating *in vacuo*. The residue was purified by chromatography (Flashmaster, 100g cartridge, eluting with dichloromethane – methanol, (9:1)) to give the *title compound* (3.38g). LCMS RT = 2.14 min

Intermediate 37

2-[3-(Cyclopentylsulfonyl)phenyl]ethanol

i) Methyl (3-mercaptophenyl)acetate

To a solution of 3-mercaptophenylacetic acid (2g) in methanol (140mL) was added hydrochloric acid (37%, 1.35mL) dropwise. The reaction mixture was stirred at room temperature, under nitrogen for 17 h. The reaction mixture was concentrated *in vacuo* and the residue azeotroped with methanol. The residue was purified by chromatography (SPE, 50g cartridge, eluting with cyclohexane – ethyl acetate mixture) to give the *title compound* (0.79g). LCMS RT = 2.76 min

ii) Methyl [3-(cyclopentylthio)phenyl]acetate

A solution of methyl (3-mercaptophenyl)acetate (200mg) and cyclopentyl bromide (491mg) in anhydrous DMF(10mL) was cooled to 0°C. Sodium hydride (60% dispersion in oil, 53.2mg) was added portionwise. Stirring was continued at 0°C for 30 min and was then allowed to warm to room temperature over 4 h. Water was added to the reaction followed with DCM and aqueous sodium bicarbonate solution. The organic layer washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed

on a Biotage cartridge (8g) eluting with cyclohexane – ethyl acetate, (5:1) to give the *title compound* (185mg) LCMS RT = 3.48 min

iii) Methyl [3-(cyclopentylsulfonyl)phenyl]acetate

To a solution of methyl [3-(cyclopentylthio)phenyl]acetate (180mg) in dichloromethane (2mL) at 0°C was added 3-chloroperoxybenzoic acid (456mg). The reaction mixture was then stirred at room temperature, under nitrogen, for 5 h. The reaction mixture was then washed with sodium bisulphite solution. The organic layer was passed through a column of Alumina (activated, neutral, Brockmann1, standard grade) eluting with cyclohexane – ethyl acetate, (1:1) and concentrated *in vacuo* to give the *title compound* (81.9mg) LCMS RT = 2.76 min

iv) 2-[3-(Cyclopentylsulfonyl)phenyl]ethanol

To a solution of methyl [3-(cyclopentylsulfonyl)phenyl]acetate (81mg) in anhydrous THF (3mL) was added lithium aluminium hydride (1 M solution in diethyl ether, 0.172mL) at room temperature. After 15 min THF followed with dichloromethane and water were added. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resultant residue was chromatographed on a Biotage cartridge and eluted with ethyl acetate – cyclohexane, (2:1) to give the *title compound* (36.4mg). LCMS RT = 2.43 min ES+ve 255 $(MH)^+$

Intermediate 38

4-[3-(Cyclopentylsulfonyl)phenyl]butan-1-ol

i) 1-(Cyclopentylthio)-3-iodobenzene

To a solution of 1-bromo-3-(cyclopentylthio)benzene (117.5g) in THF (1000mL) at –72°C was added butyllithium (1.6M in hexanes, 328mL). When addition was completed a solution of iodine (139g) in THF (300mL) was added dropwise. The reaction mixture was then allowed to warm to 0°C. Water was added cautiously and the mixture partitioned between ethyl acetate and aqueous sodium thiosulphate. The aqueous phase was extracted with ethyl acetate and the combined organics were washed with sodium thiosulphate, water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* (126.4g). HPLC RT = 2.17 min

ii) 1-(Cyclopentylsulfonyl)-3-iodobenzene

To a solution of 1-(cyclopentylthio)-3-iodobenzene (112.1g) in dichloromethane (1600mL) at 0°C was added 3-chloroperoxybenzoic acid (278g) portionwise. After 2.25 h water followed with dichloromethane were added to the reaction mixture. The aqueous phase was extracted with dichloromethane and the combined organics were washed with 1M sodium hydroxide, sodium metabisulphite and water. This was then filtered through Celite and then washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The resultant residue was dissolved in diethyl ether, washed with 2M sodium hydroxide, water and brine, dried ($MgSO_4$) and evaporated in vacuo to give the *title compound* (90g). LCMS RT = 3.27 min

Intermediate 39

4-[3-(Methylsulfonyl)phenyl]butan-1-ol

i) *tert*-Butyl(dimethyl){4-[3-(methylsulfonyl)phenyl]butoxy}silane

(But-3-enyloxy)(*tert*-butyl)dimethylsilane (**Angew Chem**, 2003, **42**, 2521) (1.68g) was stirred with 9-borabicyclo[3.3.1]nonane (0.5M in THF, 22mL) in THF(36mL) at 21° under nitrogen for 2.5 h. Potassium phosphate (3.87g) in water (5.4mL) was added followed by palladium acetate (25mg), triphenylphosphine (48mg) and 1-bromo-3-(methylsulfonyl)benzene (2.12g) and stirring was continued for 20 h. The solution was partitioned between water and ethyl acetate. The aqueous layer was extracted with further ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography twice on silica gel in mixtures of ethyl acetate in 40-60 petroleum ether to give the impure *title compound* (0.65g), nmr, δ ($CDCl_3$) 7.78 (2H, br s), 7.52 - 7.47 (2H, m),.3.64 (2H, t, J 6 Hz), 3.06 (3H, s), 2.74 (2H, t J 7 Hz), 1.89 - 1.45 (4H + water, m), 0.89 (9H, s) 0.05 (6H, s).

ii) 4-[3-(Methylsulfonyl)phenyl]butan-1-ol

tert-Butyl(dimethyl){4-[3-(methylsulfonyl)phenyl]butoxy}silane (0.62g) was stirred with tetrabutylammonium fluoride on silica gel (6.8g) in THF (70mL) for a total of three days. The mixture was filtered and the filter cake was leached with ethyl acetate. The combined filtrates were evaporated and the residue was purified by chromatography on silica gel in ethyl acetate followed by 10% methanol in ethyl acetate to give the *title compound* (0.30g). LCMS RT= 2.21 min.

Example 13:

Formic acid compound with 3-[4-({3-[2-({(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)butyl]benzenesulfonamide (1:1)

i) 3-{4-[(3-{2-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl)oxy]butyl}benzenesulfonamide

A solution of 3-(4-hydroxybutyl)benzenesulfonamide (11.47mg) in DCM (2mL) was treated with $NaOH_{(aq)}$ (40% w/v, 0.5mL) with rapid stirring. A solution of (5*R*)-3-{2-[3-(bromomethyl)phenyl]ethyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (27mg) in DCM (2mL) was added followed by tetra-n-butylammonium sulphate (1.4mg). The reaction mixture was heated at 43°C for 16 h. The reaction mixture was separated by hydrophobic frit and the organic phase evaporated under nitrogen to give the *title compound*. LCMS RT = 4.46 min

ii) 3-[4-({3-[2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)butyl]benzenesulfonamide

A solution of 3-{4-[(3-{2-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl)oxy]butyl}benzenesulfonamide in dry THF (2mL) was treated with potassium trimethylsilanolate (40mg) and the reaction mixture heated to 75°C for 1h. The resultant solution was applied to the top of an SCX-2 ion exchange cartridge (0.5g, preconditioned with MeOH). The cartridge was washed with MeOH (2.5mL) and left for 1h followed by elution with 2N NH_3 in MeOH (2.5mL) and Mass directed preparative HPLC afforded the *title compound*. LCMS RT = 2.34 min ES+ve m/z 529 $(MH)^+$

Similarly prepared were:

Example No.	Name	Intermediate method	Step 1 LCMS RT	LCMS RT	ES+ve m/z
14	Formic acid compound with 3-{[2-({3-[2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)ethoxy]methyl} benzonitrile (1:1)	Intermediate 1 General Method A	3.47	2.50	477
15	Formic acid compound with 4-[(1R)-2-({2-[3-({2-[(2,6-dichlorobenzyl)oxy]ethoxy}methyl)	General Method A	3.78	2.75	520

	phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)				
16	Formic acid compound with_4-[(1R)-2-({2-[3-({2-[(3-fluorobenzyl)oxy]ethoxy}methyl)pheny]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)	General Method A	3.58	2.58	470
17	Formic acid compound with_4-[(1R)-2-({2-[3-({2-[(3,5-dimethylbenzyl)oxy]ethoxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1) GSK206904A	General Method A	3.76	2.72	4.80
18	Formic acid compound with_4-[(1R)-1-hydroxy-2-({2-[3-({2-[(3-methoxybenzyl)oxy]ethoxy}methyl)phenyl]ethyl}amino)ethyl]-2-(hydroxymethyl)phenol (1:1)	General Method A	3.54	2.52	482
19	Formic acid compound with_2-(hydroxymethyl)-4-{(1R)-1-hydroxy-2-[(2-{3-[(2-{[3-(trifluoromethoxy)benzyl]oxy}ethoxy)methyl]phenyl}ethyl)amino]ethyl}phenol (1:1)	General Method A	3.76	2.82	536
20	Formic acid compound with_4-((1R)-1-hydroxy-2-{[2-(3-{[4-(3-hydroxyphenyl)butoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol (1:1)	Intermediate 2 General Method B	3.72	2.18	466
21	Formic acid compound with_4-[3-({3-[2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amin	General Method B	3.59	2.21	461

	o)ethyl]benzyl}oxy)propyl]benzonitrile (1:1)				
22	Formic acid compound with_4-[4-({3-[2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)butyl]benzonitrile (1:1)	General Method B	3.67	2.30	475
23	Formic acid compound with_3-[3-({3-[2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)propyl]benzonitrile (1:1)	General Method B	3.57	2.21	461
24	Formic acid compound with_2-(hydroxymethyl)-4-[(1R)-1-hydroxy-2-({2-[3-({3-[4-(methylsulfonyl)phenyl]propoxy}methyl)phenyl]ethyl}amino)ethyl]phenol (1:1)GSK208151A	Intermediate 3 General Method C	3.38	2.46	514
25	Formic acid compound with_2-(hydroxymethyl)-4-[(1R)-1-hydroxy-2-({2-[3-({[4-(methylsulfonyl)benzyl]oxy}methyl)phenyl]ethyl}amino)ethyl]phenol (1:1)	General Method C	3.27	2.34	486
26	Formic acid compound with_4-((1R)-1-hydroxy-2-{[2-(3-{[2-(2-hydroxyphenyl)ethoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol (1:1)	Intermediate 4 General Method D	4.11	2.44	438
27	Formic acid compound with_4-((1R)-1-hydroxy-2-{[2-(3-{[(4-hydroxybenzyl)oxy]methyl}phenyl)ethyl]amino}ethyl)-2-	General Method D	4.06	2.38	424

	(hydroxymethyl)phenol (1:1)				
28	Formic acid compound with_4-((1R)-1-hydroxy-2-{[2-(3-{[3-(2-hydroxyphenyl)propoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol (1:1)	General Method C & D	4.10	2.44	438
29	Formic acid compound with_4-((1R)-1-hydroxy-2-{[2-(3-{[3-(3-hydroxyphenyl)propoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol (1:1)	General Method C & D	.16	2.5	452
30	Formic acid compound with_4-[(1*R*)-2-({2-[3-({4-[4-(cyclopentylsulfonyl)phenyl]butoxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)	General Method E & B	3.73	2.38	582
31	Formic acid compound with_4-[(1*R*)-2-({2-[3-({3-[4-(cyclopentylsulfonyl)phenyl]propoxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)	General Method E & B	3.65	2.30	568
32	Formic acid compound with_4-[(1*R*)-2-({2-[3-({3-[3-(cyclopentylsulfonyl)phenyl]propoxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)	General Method E & B	3.65	2.29	568
33	Formic acid compound with_4-[(1R)-1-hydroxy-2-({2-[3-({2-[(3-hydroxybenzyl)oxy]ethoxy}methyl)phenyl]ethyl}amino)ethyl]-2-(hydroxymethyl)phenol (1:1)	Intermediate 26	4.03	2.34	468
34	Formic acid compound with_4-	Intermediate	3.48	2.52	482

	((1R)-1-hydroxy-2-{[2-(3-{[4-(6-methoxypyrazin-2-yl)butoxy]methyl}phenyl)ethyl]amino}ethyl)-2-(hydroxymethyl)phenol (1:1)	27			
35	Formic acid compound with 4-{(1R)-2-[(2-{3-[(2-{[3-(cyclopentylsulfonyl)benzyl]oxy}ethoxy)methyl]phenyl}ethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1)	Intermediate 28	3.52	2.60	584
36	4 Formic acid compound with -{(1R)-2-[(2-{3-[(2-{[3-(cyclopentylsulfinyl)benzyl]oxy}ethoxy)methyl]phenyl}ethyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1)	Intermediate 29	3.41	2.58	568
37	Formic acid compound with 4-[(1*R*)-2-({2-[3-({[3-(cyclopentylsulfonyl)benzyl]oxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)	Intermediate 30	3.56	2.18	540
38	Formic acid compound with 4-[(1R)-2-({2-[3-({4-[3-(cyclopentylsulfinyl)phenyl]butoxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)	Intermediate 31	3.61	2.71	566
39	Formic acid compound with 3-[4-({3-[2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)butyl]benzonitrile (1:1)	Commercial intermediate	3.49	2.29	475

40	Formic acid compound with 2-(hydroxymethyl)-4-{(1R)-1-hydroxy-2-[(2-{3-[(2-phenoxyethoxy)methyl]phenyl}ethyl)amino]ethyl}phenol (1:1)	Commercial intermediate	3.58	2.52	438
41	Formic acid compound with 4-((1R)-2-{[2-(3-{[2-(3-fluorophenyl)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Commercial Intermediate	3.65	2.63	4.40
42	Formic acid compound with 4-((1R)-2-{[2-(3-{[2-(4-fluorophenyl)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Commercial Intermediate	3.63	2.64	440
43	Formic acid compound with 4-((1R)-2-{[2-(3-{[2-(2-fluorophenyl)ethoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Commercial Intermediate	3.65	2.63	440
44	Formic acid compound with 3-[({3-[2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)methyl]benzonitrile (1:1)	Commercial Intermediate	3.48	2.5	433
45	Formic acid compound with 4-[({3-[2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)methyl]benzonitrile (1:1)	Commercial Intermediate	3.48	2.51	433
46	Formic acid compound with 2-(hydroxymethyl)-4-[(1R)-1-hydroxy-2-({2-[3-({[(1R)-1-	Commercial Intermediate	3.67	2.63	422

	phenylethyl]oxy}methyl)phenyl]ethyl}amino)ethyl]phenol (1:1)				
47	Formic acid compound with_2-(hydroxymethyl)-4-[(1R)-1-hydroxy-2-({2-[3-({[(1S)-1-phenylethyl]oxy}methyl)phenyl]ethyl}amino)ethyl]phenol (1:1)	Commercial Intermediate	3.65	2.18	422
48	Formic acid compound with_4-((1R)-2-{[2-(3-{[(3,5-dimethylbenzyl)oxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Commercial Intermediate	3.76	2.73	436
49	Formic acid compound with_4-((1R)-2-{[2-(3-{[(2,6-dichlorobenzyl)oxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Commercial Intermediate	3.78	2.72	478
50	Formic acid compound with_4-((1R)-2-{[2-(3-{[(1-benzyl-1H-imidazol-2-yl)methoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Commercial Intermediate	2.51	2.09	488
51	Formic acid compound with_4-((1R)-2-{[2-(3-{[(2-fluorobenzyl)oxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Commercial Intermediate	3.59	2.12	426
52	Formic acid compound with_4-((1R)-2-{[2-(3-{[(3-fluorobenzyl)oxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Commercial Intermediate	3.59	2.58	4.26
53	Formic acid compound with_4-((1R)-2-{[2-(3-{[(4-	Commercial Intermediate	3.61	2.13	426

	fluorobenzyl)oxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)				

Example 54 :

Formic acid compound with 3-[4-({3-[2-({(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)butyl]benzamide (1:1)

i) 3-{4-[(3-{2-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl)oxy]butyl}benzonitrile

Prepared similarly to Example 13 (i). LCMS RT = 2.01 min

ii) Formic acid compound with 3-[4-({3-[2-({(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)butyl]benzamide (1:1)

A solution of crude 3-{4-[(3-{2-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl)oxy]butyl}benzonitrile in dry THF (2mL) was treated with potassium trimethylsilanolate (40mg) and the reaction mixture heated to 150°C for 2 min in a microwave (150 watts). The resultant solution was applied to the top of an SCX-2 ion exchange cartridge (0.5g, preconditioned with MeOH). The cartridge was washed with MeOH (2.5mL) and left for 1hr. The title compound was eluted with 2N NH_3 in MeOH (2.5mL). Mass directed preparative HPLC afforded the title compound. LCMS RT= 2.47 min ES+ve m/z 493 $(MH)^+$

Similarly prepared were:

Example No	Name	Step 1 LCMS RT	LCMS RT	ES+ve m/z
55	Formic acid compound with 3-{[2-({3-[2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)ethoxy]methyl}benzamide (1:1)	3.47	2.28	495
56	Formic acid compound with 3-[({3-[2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)methyl]benzamide (1:1)	3.48	2.26	451

57	Formic acid compound with 4-[({3-[2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)methyl]benzamide (1:1)	3.48	2.26	451

Example 58:

Formic acid compound with 3-[2-({3-[2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)ethyl]benzenesulfonamide (1:1)

i) 3-{2-[(3-{2-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl)oxy]ethyl}-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

A solution of 3-(2-hydroxyethyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl} benzenesulfonamide (86mg) in DCM (1.5mL) was treated with $NaOH_{(aq)}$(40% w/v, 0.5mL) with rapid stirring. A solution of (5*R*)-3-{2-[3-(bromomethyl)phenyl]ethyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (100mg) in DCM (0.5mL) was added followed by tetrabutylammonium bromide (6mg). The reaction mixture was heated at 40°C for 16 h. the reaction mixture was separated by hydrophobic frit and the organic phase evaporated under nitrogen to give the *title compound.* LCMS RT = 3.35min

ii) 3-(2-{[3-(2-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}ethyl)benzyl]oxy}ethyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

A solution of 3-{2-[(3-{2-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl)oxy]ethyl}-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide in dry THF (1mL) was treated with potassium trimethylsilanolate (215mg) and the reaction mixture heated to 75°C for 4h. After cooling, DCM (1mL) was added followed with 2N sodium bicarbonate solution (1mL). The reaction mixture was separated by hydrophobic frit and the organic phase evaporated under nitrogen to give the *title compound.* LCMS RT= 3.61min

iii) Formic acid compound with 3-[2-({3-[2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)ethyl]benzenesulfonamide (1:1)

A solution of 3-(2-{[3-(2-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}ethyl)benzyl]oxy}ethyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide in acetic acid (1mL) and water (1mL) was heated at 70°C for 10 h. The reaction mixture was evaporated under nitrogen and

Mass directed preparative HPLC afforded the *title compound*. LCMS RT = 2.20 min ES+ve 501 $(MH)^+$

Similarly prepared were:

Examples 59-62. For the compounds of Examples 60, 61 and 62 reaction mixtures in acetic acid and water were heated at 70°C for 45 min:

Similarly prepared were:

Example No.	Name	Intermediate method	Step (i) LCMS RT	Step (ii) LCMS RT	LCMS RT	ES +ve m/z
59	Formic acid compound with 3-[3-({3-[2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)propyl]benzenesulfonamide (1:1)	Intermediate 34	4.47	3.60	2.28	515
60	Formic acid compound with 4-((1*R*)-2-{[2-(3-{[4-(2,6-dichlorophenyl)butoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)	Intermediate 35	4.11	3.19	2.90	518
61	Formic acid compound with *N*-{3-[4-({3-[2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)butyl]phenyl}urea (1:1)	Intermediate 36	2.98	2.40	2.12	508
62	Formic acid compound with 2-(hydroxymethyl)-4-((1*R*)-1-hydroxy-2-{[2-(3-{[2-(1-phenylethoxy)ethoxy]methyl}phenyl)ethyl]amino}ethyl)phenol	CAS 4799-66-0	3.67	2.76	2.46	466

	(1:1)					

Example 63

Formic acid compound with 4-[(1*R*)-2-({2-[3-({2-[3-(cyclopentylsulfonyl)phenyl]ethoxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)

(i) (5*R*)-3-{2-[3-({2-[3-(Cyclopentylsulfonyl)phenyl]ethoxy}methyl)phenyl]ethyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Sodium hydride (9mg) was added to a solution of 2-[3-(cyclopentylsulfonyl)phenyl]ethanol (41mg) in dry DMF (0.5mL). A solution of (5*R*)-3-{2-[3-(bromomethyl)phenyl]ethyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (100mg) in dry DMF (0.5mL) was added and stirring was continued for 16 h at room temperature. Water (0.5mL) was added followed by dichloromethane (1mL). The reaction mixture was separated by hydrophobic frit and the organic phase evaporated under nitrogen to give the *title compound.*

LCMS RT = 3.63 min.

(ii) (5*R*)-3-{2-[3-({2-[3-(Cyclopentylsulfonyl)phenyl]ethoxy}methyl)phenyl]ethyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Prepared similarly to example 58 (ii) LCMS RT = 2.82 min

(iii) Formic acid compound with 4-[(1*R*)-2-({2-[3-({2-[3-(cyclopentylsulfonyl)phenyl]ethoxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)

Prepared similarly to example 58 (iii).

LCMS RT = 2.56 min. ES+ve m/z 554 $(MH)^+$

Similarly prepared were:

Example No.	Name	Intermediate Method	Step (i) LCMS RT	Step (ii) LCMS RT	LCMS RT	ES +ve m/z

64	Formic acid compound with 4-[(1*R*)-2-({2-[3-({4-[3-(cyclopentylsulfonyl)phenyl]butoxy}methyl)phenyl]ethyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (1:1)	Intermediate 38	3.75	2.94	2.65	582
65	Formic acid compound with 2-(hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({2-[3-({4-[3-(methylsulfonyl)phenyl]butoxy}methyl)phenyl]ethyl}amino)ethyl]phenol (1:1)	Intermediate 39	3.51	2.74	2.42	528

Example 66:

Formic acid compound with 4-((1*R*)-2-{[2-(3-{[3-(2,6-dichlorophenyl)propoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)

i) (5*R*)-3-[2-(3-{[3-(2,6-Dichlorophenyl)propoxy]methyl}phenyl)ethyl]-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Sodium hydride (7.3mg) was added to a stirred solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{2-[3-(hydroxymethyl)phenyl]ethyl}-1,3-oxazolidin-2-one (50mg) in anhydrous DMF (2ml). A solution of 2-(3-bromopropyl)-1,3-dichlorobenzene (CAS 14573-25-2) (48.7mg) in anhydrous DMF (2mL) was added and stirring was continued at room temperature, under nitrogen for 60 h. Water was added followed by DCM (1mL). The reaction mixture was separated by hydrophobic frit and the organic phase evaporated under nitrogen to give the *title compound*. LCMS RT = 4.01 min

ii) (1*R*)-2-{[2-(3-{[3-(2,6-Dichlorophenyl)propoxy]methyl}phenyl)ethyl]amino}-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

Prepared using similar methods to those in General Method B ii) LCMS RT = 3.09 min

iii) Formic acid compound with 4-((1R)-2-{[2-(3-{[3-(2,6-dichlorophenyl)propoxy]methyl}phenyl)ethyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)

Prepared using similar methods to those in Example 58 iii) LCMS RT = 2.79 min ES+ve m/z 504

Example 67:

3-[({3-[2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)methyl]benzenesulfonamide acetate

i) 3-{[(3-{2-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}benzyl)oxy]methyl}-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

Prepared with Intermediate 32 and CAS 503068-53-9 using similar methods to those in Example 58 i) LCMS RT = 4.42 min

ii) 3-({[3-(2-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}ethyl)benzyl]oxy}methyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

Prepared using similar methods to those in Example 58 ii) LCMS RT = 3.57 min

iii) 3-[({3-[2-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)ethyl]benzyl}oxy)methyl]benzenesulfonamide acetate

A solution of 3-({[3-(2-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}ethyl)benzyl]oxy}methyl)-*N*,*N*-bis{[2-(trimethylsilyl)ethoxy]methyl} benzenesulfonamide (100mg) in acetic acid (6mL) and water (2mL) was heated at 70°C, under nitrogen for 5 h. The reaction was then concentrated *in vacuo* and the residue chromatographed on a Biotage cartridge (12g) eluting with dichloromethane – ethanol – ammonia solution (100:8:1, then 50:8:1) to give the *title compound* (3mg) LCMS RT = 2.20 min

ES+ve 487 $(MH)^+$

BIOLOGICAL ACTIVITY

In vitro measurements of compound potency and intrinsic activity at the human Beta 1, 2 and 3 receptors.

Method 1

The potencies of the compounds of Examples 1-12 were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of said examples had IC_{50} values below 1 μM.

Method 2

Potency of compounds of the invention at the human beta 2, 1 and 3 receptors was also determined using Chinese hamster ovary cells co-expressing the human receptor with a reporter gene. Studies were performed using either whole cells or membranes derived from those cells.

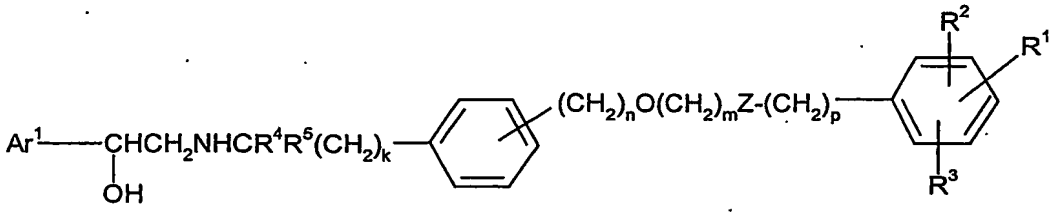
The three beta-receptors are coupled *via* the Gs G-protein to cause a stimulation of adenylate cyclase resulting in increased levels of cAMP in the cell. For direct cAMP measurements either membranes or cells have been used with either the HitHunter enzyme fragment complementation kit (DiscoveRx) or the FP^2 fluorescence polarisation kit (Perkin Elmer) to quantify the levels of cAMP present. These assays provide a measure of agonist potency and intrinsic activity of the compounds at the various receptors.

The reporter gene in the cells has also been used to quantify potency at the beta 1 and 3 receptors. This is a reporter of cAMP levels using the cAMP response element upstream of a firefly luciferase gene. After stimulation of the receptor with an agonist an increase in the level of luciferase is measured as a quantification of the level of cAMP in the cell.

In this assay the potency of compounds at the human beta-2 receptor is expressed as a pEC_{50} value.

Claims

A compound of formula (I):



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

k is an integer from 1 to 3;

n is an integer of from 1 to 4;

m is an integer of from 2 to 4;

p is an integer of from 1 to 4, preferably 1;

Z is O or CH_2-

R^1 is selected from hydrogen, C_{1-6}alkyl, hydroxy, cyano, nitro, halo, C_{1-6}haloalkyl, XCO_2R^8, $-XC(O)NR^7R^8$, $-XNR^6C(O)R^7$, $-XNR^6C(O)NR^7R^8$, $-XNR^6C(O)NC(O)NR^7R^8$, $-XNR^6SO_2R^7$, $-XSO_2NR^9R^{10}$, XSR^6, $XSOR^6$, XSO_2R^6, $-XNR^7R^8$, $-XNR^6C(O)OR^7$,

or R^1 is selected from -X-aryl, -X-hetaryl, or -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, $-NR^6C(O)R^7$, SR^6, SOR^6, $-SO_2R^6$, $-SO_2NR^9R^{10}$, $-CO_2R^8$, $-NR^7R^8$, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

X is $-(CH_2)_q-$ or C_{2-6} alkenylene;

q is an integer from 0 to 6, preferably 0 to 4;

R^6 and R^7 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)- and R^6 and R^7 are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, -NHC(O)(C_{1-6}alkyl), -SO_2(C_{1-6}alkyl), -SO_2(aryl), -CO_2H, and -CO_2(C_{1-4}alkyl), -NH_2, -NH(C_{1-6}alkyl), aryl(C_{1-6}alkyl)-, aryl(C_{2-6}alkenyl)-, aryl(C_{2-6}alkynyl)-, hetaryl(C_{1-6}alkyl)-, -$NHSO_2$aryl, -NH(hetarylC_{1-6}alkyl), -$NHSO_2$hetaryl, -$NHSO_2$(C_{1-6}alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

R^8 is selected from hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl;

or R^7 and R^8, together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered nitrogen – containing ring;

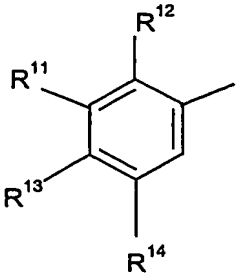
R^9 and R^{10} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)-, or R^9 and R^{10}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring; and R^9 and R^{10} are each optionally substituted by one or two groups independently selected from halo, C_{1-6}alkyl, and C_{3-7}cycloalkyl, C_{1-6}haloalkyl;

R^2 is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo, aryl, aryl(C_{1-6}alkyl)-, C_{1-6}haloalkoxy, and C_{1-6}haloalkyl;

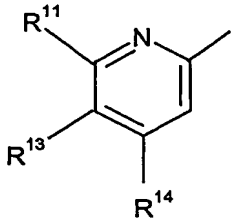
R^3 is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo, aryl, aryl(C_{1-6}alkyl)-, C_{1-6}haloalkoxy, and C_{1-6}haloalkyl; and

R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4

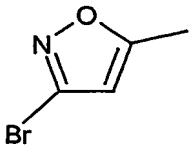
Ar^1 is a group selected from



(a)

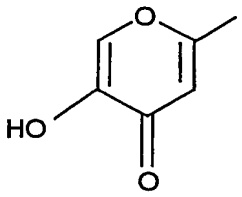


(b)



(c)

and



(d)

wherein R^{11} represents halogen, $-(CH_2)_rOR^{15}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}SO_2R^{16}$, $-SO_2NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$,
and R^{12} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{11} represents $-NHR^{18}$ and R^{12} and $-NHR^{18}$ together form a 5- or 6- membered heterocyclic ring;

R^{13} represents hydrogen, halogen, $-OR^{15}$ or $-NR^{15}R^{16}$;

R^{14} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{15}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$

R^{15} and R^{16} each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$ and $-OC(O)NR^{15}R^{16}$, R^{15} and R^{16} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{17} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

r is zero or an integer from 1 to 4.

2. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

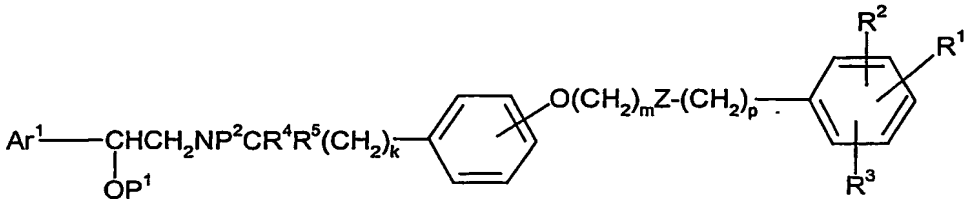
3. A compound of formula (I), according to claims 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

4. A pharmaceutical formulation comprising a compound of formula (I), according to claim 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

5. The use of a compound of formula (I), according to claim 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated.

6. A process for the preparation of a compound of formula (I), according to claim 1, or a salt, solvate, or physiologically functional derivative thereof, which comprises:

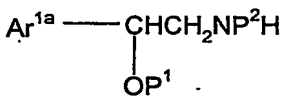
(a) deprotection of a protected intermediate, for example of formula (II):



(II)

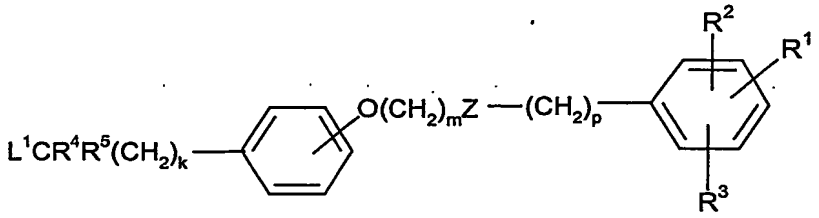
or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, Z, k, m, n and p are as defined for the compound of formula (I), Ar^{1a} is Ar^1 or a protected form thereof and P^1 and P^2 each independently represents hydrogen or a protecting group provided that the compound of formula (II) contains at least one protecting group; or

(b) alkylation of an amine of formula (X)



(X)

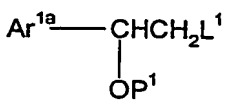
wherein Ar^{1a} is as hereinbefore defined P^2 and P^1 are each independently either hydrogen or a protecting group,
with a compound of formula (XI):



(XI)

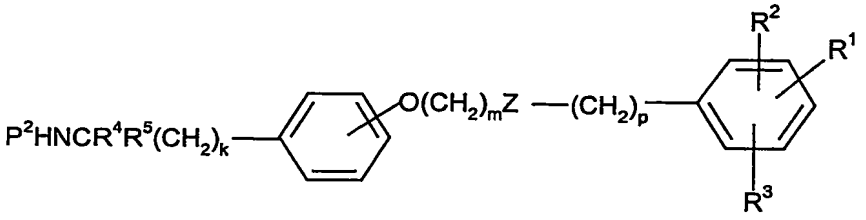
wherein R^1, R^2, R^3, R^4, R^5, Z, k, m, n and p are as defined for the compound of formula (I) and L^1 is a leaving group;

(c) reacting a compound of formula (XII):



(XII)

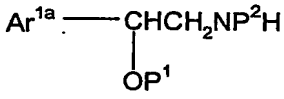
wherein Ar^1 and P^1 are as hereinbefore defined and L^1 is a leaving group, with an amine of formula (XIII):



(XIII)

or

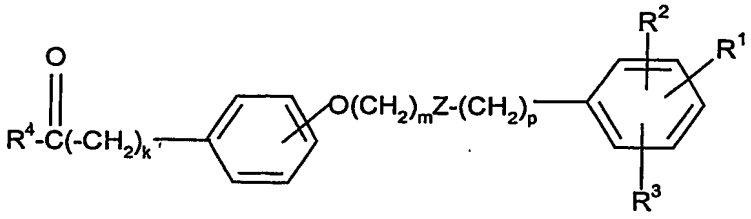
d) reacting a compound of formula (X):



(X)

as hereinbefore defined,

with a compound of formula (XIV):



(XIV)

under conditions suitable to effect reductive amination;

followed by the following steps in any order:

(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate,

or physiologically functional derivative thereof.